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Validating a Practical Correction for Intravenous Contrast on Computed Tomography–Based Muscle Density

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Objective: Computed tomography (CT) measured muscle density is prognostic of health outcomes. However, the use of intravenous contrast obscures prognoses by artificially increasing CT muscle density. We previously established a correction to equalize contrast and noncontrast muscle density measurements. While this correction was validated internally, the objective of this study was to obtain external validation using different patient cohorts, muscle regions, and CT series.

Methods: CT images from 109 patients with kidney tumors who received abdominal CT scans with a multiphase intravenous contrast protocol were analyzed. Paraspinal muscle density measurements taken during noncontrast, venous phase, and delayed phase contrast scans were collected. An *a priori* correction of −7.5 Hounsfield units (HU) was applied to muscle measurements. Equivalence testing was utilized to determine statistical similarity.

Results: In the sample of 109 patients (mean age: 63 years [SD: 14.3]; 41.3% female), densities in smaller regions of interest within the paraspinal muscles and the entire paraspinal muscle density (PS) in venous and delayed phase contrast scans were higher than in noncontrast. Equivalence testing showed that average corrected contrast and noncontrast muscle densities were within 3 HU for both muscle measures for the total patient sample, and for a majority of male and female subsamples. The correction is suitable for regions of interests of venous contrast (90% CI: −1.90, −0.69 HU) and delayed contrast scans (90% CI: 0.075, 1.29 HU) and within the PS measures of venous contrast (90% CI: −2.04, −0.94 HU) and delayed contrast scans (90% CI: −0.11, 0.89 HU)

Conclusions: The previously established correction for contrast of −7.5 HU was applied in a new patient population, axial muscle region, muscle measurement size, and expanded on previously studied contrast phases. The correction produced contrast-corrected muscle densities that were statistically equivalent to noncontrast muscle densities. The simplicity of the correction gives clinicians a tool that seamlessly integrates into practice or research to improve harmonization of data between contrast and noncontrast scans.

Key Words: muscle density, Hounsfield units, paraspinal muscle, intravenous contrast, correction validation, computed tomography

Abbreviations ROI - region of interest within the paraspinal muscle, PS - whole paraspinal muscle measurement, NC - noncontrast, VC - venous phase contrast, DC - delayed phase contrast, CT - computed tomography, IV - intravenous, SD - standard deviation, CI - confidence interval, HU - Hounsfield unit, kV - kilovolts

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BACKGROUND

Computed tomography (CT) is a vital diagnostic tool in healthcare, with applications ranging from routine clinical care to surgical preparation. CT's utility extends to muscle health assessment, where it accurately discriminates muscle from surrounding tissue.[1,2] Muscle density, as a surrogate of muscle quality, is a critical indicator for various health conditions such as muscular dystrophy, cachexia, sarcopenia, and myosteatosis.[3–5] CT muscle density is quantified in Hounsfield units (HU), which is derived from the attenuation of x-rays passing through tissues. This allows for identification of fatty infiltration of muscle which lowers HU, indicating muscle wasting or degeneration.[6–8]

Importantly, due to the perceived risk of radiation exposure associated with CT scans, assessment of muscle health with CT is currently limited to opportunistic evaluation of existing medical scans. The largest limitation to retrospectively reviewing opportunistic CT scans is the variation in scan protocol; of particular importance is the presence or absence of IV contrast at the time of the scan.[9] The use of IV contrast material increases the attenuation of X-rays by the muscle, leading to an overestimation of muscle density.[10] The degree of this overestimation may vary based on several factors, including the type and volume of contrast material used and the timing of the scan in relation to contrast administration (contrast phase).[10–12] Therefore, muscle density measurements from contrast-enhanced and noncontrast-enhanced scans should not be used interchangeably without accounting for this change in HU. Failure to account for this discrepancy may lead to inaccurate diagnoses and ineffective treatment plans.

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In a previous study, our group examined the effects of contrast material administered at different phases and developed a practical correction factor for muscle density in contrast-enhanced CT scans by subtracting 7.5 HU from contrast-enhanced scans.[13] This correction was validated in a subset of the same population and found that it successfully rendered muscle density statistically equivalent between contrast-enhanced and noncontrast-enhanced tissue.[13] This correction worked well independently of sex or contrast phase, and a more complicated multivariate regression correction did not correct contrast significantly better than the practical and more simplistic −7.5 HU subtraction correction. However, it is unclear whether this correction is applicable to other patient populations, muscle groups, or CT protocols. Determining the generalizability of our correction will bring us closer to its universal application in muscle measurements and may overcome a significant limitation of using CT scans as a diagnostic tool. Therefore, the aim of this study was to test the validity of the *a priori* correction for contrast enhancement on a new patient population, incorporating a different CT imaging and contrast protocol, and a novel, whole muscle group measurement for broader generalization. We hypothesize that this correction factor may be broadly applicable, not only as a means to standardize CT muscle measurements, but also serving as an implementable and clinically relevant practice.

METHODS

CT Scan Identification

Multiphase CT images of kidney tumor patients were obtained from the Picture Archiving and Communication System (PACS) with a waiver of consent approved by the Institutional Review Board. Consecutive patients from a single location who received abdominal contrast CT scans between November 2020 and July 2022 (n = 109) were included. Each patient's noncontrast (NC), venous contrast (VC), and delayed contrast (DC) scans were obtained, selecting the abdominal L3 multiphase images and disregarding any scans with artifact that precluded measurement of the muscle.

Patients received a weight-adjusted dose of Iohexol (300 mg/mL), administered at a rate of 3 mL/sec, followed by a 50 mL saline flush at the same rate. Patients were selected if they fell into the "typical" size category for the institution's CT protocols, with weights ranging from 58.97 kg to 113.40 kg (130–250 lb), who received a linear, weight-adjusted contrast dose between 80 mL and 150 mL.[14] Patients outside this weight range were excluded, as they received a fixed contrast dose and different acquisition beam energies, per protocol, which would result in a potentially confounding variable of varying contrast concentration in the body based on patient size. Patients were scanned on a GE Discovery HD750 (GE Healthcare, Waukesha, WI) with bowtie filters. Technical factors for NC included the following: 120 kV, helical pitch of 0.938:1, detector collimation of 16 × 1.25 mm, 3.75 mm slice thickness, noise index = 21.5. Technical factors for VC included: 120 kV_p, helical pitch of 0.938:1, detector collimation of 16 × 1.25 mm, 3.75 mm slice thickness, and noise index = 16.0. Technical factors for DC included: 120 kV_p, helical pitch of 0.562:1, detector collimation of 16 × 1.25 mm, 3.75 mm slice thickness, and noise index = 13.5. DC and VC were acquired using a Medrad P3T (Bayer, Barmen Germany) Abdomen protocol.

Images taken before IV contrast injection were used to obtain NC scans. VC and DC scans were taken 60–80 seconds and > 120 seconds after injection, respectively.

CT Skeletal Muscle Analysis

Using Osirix MD (Pixmeo, Bernex, Switzerland), 1 trained operator (DU) used the freehand ROI tool to trace the border of the entire left and right paraspinal muscles (PSs) as well as place smaller ovular ROIs of 2 cm^2 within the PSs, specifically the erector spinae, while avoiding the multifidus. This smaller ROI will hence be referred to as ROI, as they are often described in the literature in this way. This was repeated at each phase, utilizing the copy and paste functions in Osirix to maintain consistency in measurement placement, shape, and size (Fig. 1). The pasted PS and ROI measurements were adjusted if necessary for patient motion. Measurements were taken of the average skeletal muscle density of the ROIs and PS muscles, expressed in HU. A correction of −7.5 HU was applied to all VC and DC muscle HU measurements.

Statistical Analysis

Statistical testing was conducted in GraphPad Prism 9 (San Diego, CA). Data were summarized for NC, VC, and DC phases with mean (SD) and 95% confidence interval. Tukey's multiple comparisons paired *t* tests were conducted to compare means and account for multiple testing. This testing was conducted for ROI and PS muscle groups, and between each phase: NC, VC, and DC. An alpha level of 0.05 indicated statistical differences between groups.

After the correction was applied, two 1-sided tests (TOST) of equivalence were performed to compare the contrast and NC scans. These tests were performed in Jamovi version 2.3.28 (Sydney, Australia), using the TOSTER package. A margin of 3 HU was *a priori* set as an acceptable margin of equivalence, as similarly used in our previous study.[13] This margin was chosen according to analysis of literature and consultation with a CT physicist as a conservative number that includes an acceptable range of intraindividual CT scan variation. Indeed, Aubrey et al found that radiation attenuation of muscle on rigorously calibrated equipment was accurate to the nearest 4–5 HU.[15] For equivalence testing, an alpha level of 0.05 represents statistical equivalence.

RESULTS

Patient Characteristics

The study population was comprised of 109 kidney tumor patients. This cohort had readily available contrast and NC scans from the same day, making them an ideal population for validation testing. The cohort had an average age of 63 years (SD: 14.3) and was 41.3% female (Table 1).

Comparative Analysis of Muscle Density

Muscle density in both PS and ROI measurements were consistently higher in the VC and DC phases compared to the NC phase (Fig. 2). This was observed across all subjects, regardless of sex.

In the ROI, the VC muscle density exceeded the NC density by 8.3 ± 0.97, 4.7 ± 0.73, and 6.2 ± 0.82 HU for female, male, and total subjects, respectively ($P < 0.0001$). Similarly, the DC muscle density was higher than the NC

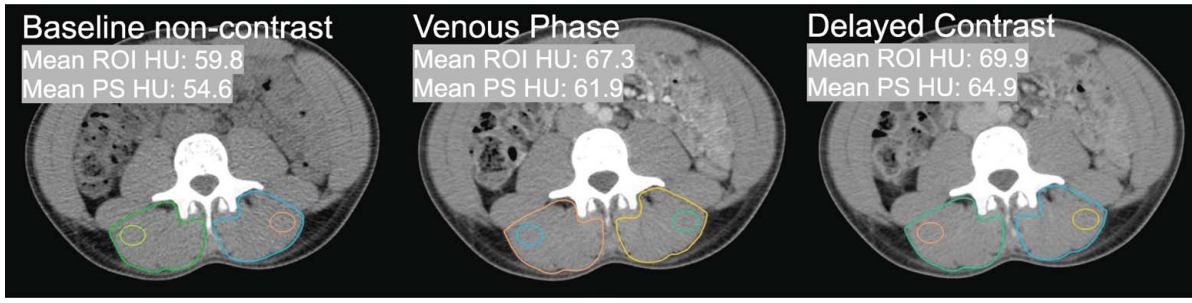

FIGURE 1. Example ROI and PS HU for NC, VC, and delayed phase contrast CT scans.

density by 9.7 ± 1.2, 7.1 ± 1.1, and 8.1 ± 1.1 HU for female, male, and total subjects, respectively ($P < 0.0001$).

In the PS, the VC muscle density was higher than the NC density by 7.5 ± 1.3, 5.0 ± 1.2, and 6.0 ± 1.2 HU for female, male, and total subjects, respectively ($P < 0.0001$). Likewise, the DC muscle density exceeded the NC density by 9.1 ± 0.9, 7.0 ± 1.3, and 7.9 ± 1.1 HU for female, male, and total subjects, respectively ($P < 0.0001$).

Equivalence Testing

In order to evaluate the accuracy of the previously established correction, equivalence testing was used to determine statistical similarity. Equivalence testing was performed using the TOSTs approach to compare muscle density measurements between NC and corrected contrast (VC* and DC*) scans, with a margin of 3 HU set as the threshold for equivalence (Table 2).

In the overall patient population, the differences between NC and contrast-enhanced scans were as follows: for the ROI measurement, the NC versus VC* comparison showed a difference of −1.29 HU (90% CI: −1.90 to −0.69, $P < 0.0001$, Fig. 3), and the NC versus DC* comparison showed an estimate difference of 0.69 HU (90% CI: 0.075 to 1.29, $P < 0.0001$). For the PS measurement, the NC versus VC* comparison showed a difference of −1.49 HU (90% CI: −2.04 to −0.94, $P < 0.0001$), and the NC versus DC* comparison showed a difference of 0.39 HU (90% CI: −0.11 to 0.89, $P < 0.0001$).

For female patients, the ROI NC versus VC* comparison showed a difference of 0.81 HU (90% CI: −0.15 to 1.76, $P = 0.0002$, Table 2). The ROI NC versus DC* comparison showed a difference of 2.17 HU (90% CI: 1.20 to 3.13, $P = 0.077$), breaching the upper limit by 0.13 HU. The PS NC versus VC* comparison showed a difference of −0.023 HU (90% CI: −0.95 to 0.91, $P < 0.0001$). The PS NC versus DC* comparison showed a difference of 1.59 HU (90% CI: 0.79 to 2.38, $P = 0.0023$).

For male patients, the ROI NC versus VC* comparison showed a difference of −2.78 HU (90% CI: −3.41 to −2.15, $P = 0.281$, Table 2), breaching the lower bound by 0.41 HU and not achieving significance. The ROI NC versus DC* comparison showed a difference of −0.36 HU (90% CI: −1.09 to 0.37, $P < 0.0001$). The PS NC versus VC* comparison showed a difference of −2.52 HU (90% CI: −3.13 to −1.92, $P = 0.097$), breaching the lower bounds by 0.13 HU. The PS NC versus DC* comparison showed a difference of −0.46 HU (90% CI: −1.05 to 0.14, $P < 0.0001$).

DISCUSSION

In this study, an *a priori* correction for contrast enhancement on muscle measurements in CT scans was successfully externally validated in our total cohort and a vast majority of subsets. First, these findings confirm a discrepancy between contrast-enhanced and NC muscle HU in this sample, consistent with previous findings in various populations. Then, the application of a −7.5 HU correction resulted in muscle HU measurements that were statistically equivalent to those obtained from NC scans. This was true for both ROIs and whole PS measurements, and across both venous and delayed phase contrast scans, with the exceptions of the male ROI NC versus VC* group, and statistical trends observed in the female ROI NC versus DC* group and the male PS NC versus VC* group. However, it can be argued that while breaching the thresholds of the equivalence test by even a relatively small amount means the P value will be higher than the alpha level, it does not necessarily mean the correction is not effective. It is more important to consider the full context of the results, including the estimate difference and confidence interval in these cases, which were very close to our conservative threshold of ±3 HU. Hence, these results suggest that a simple correction method can be effectively applied across 1) different patient populations, 2) axial CT muscle regions, and 3) contrast phases. This is a significant step toward harmonizing data from contrast-enhanced and NC CT scans, which could lead to more accurate diagnoses and improved clinical applicability of CT muscle measures.

Prior research has shown that contrast increases HU values due to higher iodine concentrations perfusing

TABLE 1. Subject Demographics and Muscle Hounsfield Units

	Female	Male	All Subjects
n	45 (41%)	64 (59%)	109
Age (y)	64.2 (16.9)	62.3 (12.2)	63.1 (14.3)
BMI	29.8 (6.7)	32.9 (8.3)	31.6 (7.8)
ROI HU values			
NC HU	26.3 (20.0)	29.8 (19.6)	28.4 (19.8)
VC HU	34.6 (21.0)	34.6 (20.4)	34.6 (20.5)
DC HU	35.9 (21.2)	37.0 (20.8)	36.5 (20.9)
PS HU values			
NC HU	14.4 (18.6)	22.7 (19.9)	19.3 (19.1)
VC HU	21.9 (19.9)	27.6 (19.9)	25.3 (20.0)
DC HU	23.5 (19.8)	29.7 (20.2)	27.2 (20.2)

All data displayed in means with SDs in parentheses, except for n, which is displayed in number and percent in parentheses.

HU, Hounsfield units; NC, non-contrast; VC, venous phase contrast; DC, delayed phase contrast.

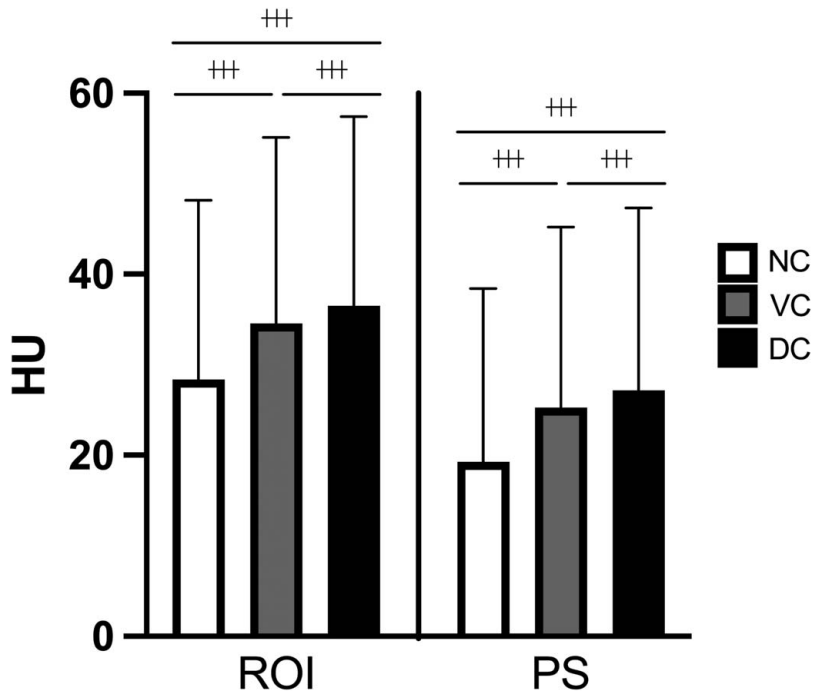

FIGURE 2. Differences Between Non-Contrast and Contrast Measurements of Muscle HU Before Correction. Muscle attenuation in Hounsfield unit (HU) measured via region of interest (ROI) and paraspinal muscle (PS) for non-contrast (NC), venous contrast (VC), and delayed phase contrast (DC) Data shown as mean +/- SD. Significance bars (+++) represent statistical differences of multiple paired *t*-tests at $P > 0.0001$.

muscle tissue, resulting in augmented attenuation values.[10,12,16] While past studies have proposed linear regression corrections for these changes,[17–19] their implementation can be cumbersome for clinicians, requiring specific applications or tools, which hinder clinical adoption. By comparison, our method employs a straightforward subtraction approach which is memorable and easily computed. Our previous findings suggest that this simple correction is just as effective as intricate calculations, while offering the added advantage of being clinically practical.[13] Our previous correction was developed in a cohort of routine abdominal CT scans, with arterial and VC phases, and at the level of the liver (majority T10-T12 axial location). A smaller ROI within the PS (similar to the ROI in this paper) was used to develop the correction. Hence, this paper validates the correction in a novel patient population (kidney tumor), novel axial location (L3), different contrast phases (venous and delayed) and larger area method of muscle measurement (PS).

TABLE 2. Equivalence Testing Between NC and Corrected Contrast Values

Total	Estimate	Lower Bound	Upper Bound	*P* Value
ROI NC vs ROI VC*	−1.29	−1.90	−0.69	< 0.0001
ROI NC vs ROI DC*	0.69	0.075	1.29	< 0.0001
PS NC vs PS VC*	−1.49	−2.04	−0.94	< 0.0001
PS NC vs PS DC*	0.39	−0.11	0.89	< 0.0001
Female				
ROI NC vs ROI VC*	0.81	−0.15	1.76	0.0002
ROI NC vs ROI DC*	2.17	1.20	3.13	0.077
PS NC vs PS VC*	−0.023	−0.95	0.91	< 0.0001
PS NC vs PS DC*	1.59	0.79	2.38	0.0023
Male				
ROI NC vs ROI VC*	−2.78	−3.41	−2.15	0.28
ROI NC vs ROI DC*	−0.36	−1.09	0.37	< 0.0001
PS NC vs PS VC*	−2.52	−3.13	−1.92	0.097
PS NC vs PS DC*	−0.46	−1.05	0.14	< 0.0001

All data displayed in Hounsfield units, Upper and lower bounds represent 90% confidence interval.

DC*, corrected delayed phase contrast; NC, non-contrast; PS, entire paraspinal muscle measurement; ROI, region of interest measurement in the paraspinal muscle; VC*, corrected venous phase contrast.

Considerations of variations in muscle area and density due to CT protocols are crucial in establishing cutoff points for the diagnosis of muscle wasting conditions such as sarcopenia, myosteatosis, cachexia, and muscular dystrophy.[20–25] Alterations in muscle HU due to contrast can potentially shift individuals across these cutoff points, particularly those near the delineation. This becomes especially pertinent as HU is a surrogate of muscle quality by virtue of its ability to represent adipose infiltration, and recent sarcopenia diagnostic guidelines advocate for the use of muscle quality and strength over quantity.

CT muscle HU as a surrogate for muscle quality offers several advantages over traditional body composition and strength assessments: it is objective, independent of patient volition, and accessible to all patients undergoing a CT scan, irrespective of their mobility and cognition. Furthermore,

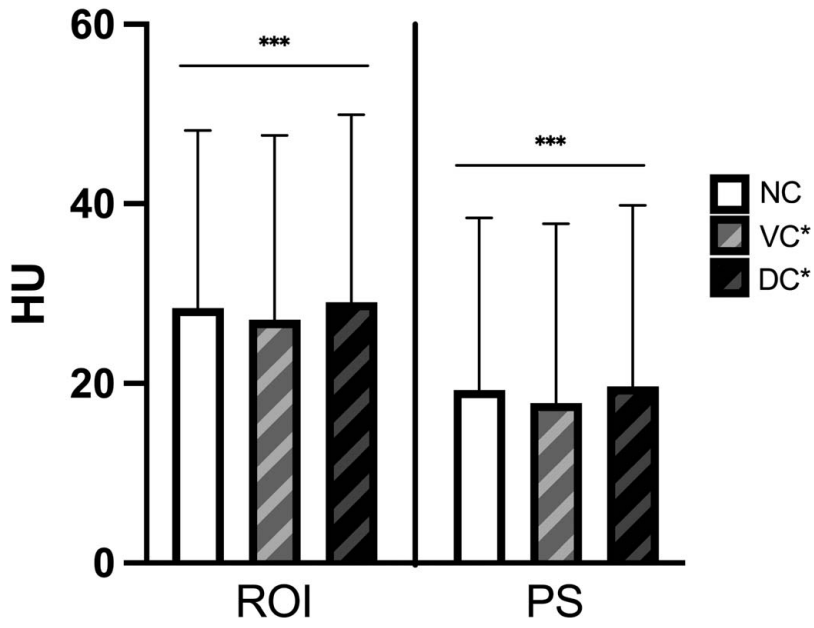

FIGURE 3. Equivalence testing of NC and corrected contrast (*) measurements of muscle HU. Comparison of mean ROI and PS HU after applying −7.5 HU correction to venous (VC*) and delayed phase (DC*) contrast CT scans shown as mean ± SD. Significance bars (***) represent statistical equivalence at 3 HU margin with $P > 0.0001$.

muscle HU has been found to be predictive of survival in numerous clinical populations, including those with heart failure,[26,27] cancer,[28,29] and COVID-19,[30] among others.[31–35] However, to effectively utilize CT muscle density as a diagnostic tool for muscle wasting diseases and a predictor of survival, it is imperative to establish cut-points for healthy muscle density that are applicable to both contrast and NC exams. Consequently, our study agrees with our previous scoping review that contrast and NC data should not be used interchangeably without consideration,[10] and we advocate that one way to solve this problem is by applying a correction factor to account for the artificial inflation of muscle density due to contrast.

Our study had some limitations. The validity of the contrast correction method in two muscle measures was examined, and it is unclear if this method would be applicable to other muscle groups or tissues. To reduce the number of variables, patients with weight-based contrast dose were included, and patients that received fixed contrast doses were omitted.[36,37] While this allowed us to avoid issues with fixed contrast dosing, this introduces bias based on patient size, as only patients between 130 and 250 lb received weight-based contrast at our institution, therefore the correction may not be applicable to patients outside that range, or with a different contrast dosing protocol. Patient size is related to another potential limitation, as patients within this range received scans with 120 kV beam energy, and the attenuation effect of contrast in muscle may be different in scans with higher or lower beam energy. Furthermore, despite different protocols as the previous study that developed the correction, similar CT scanners were used. Regarding the difference in noise indices between the three scan phases, there is a possibility that the noise may affect muscle HU at a granular level, by increasing the voxel-to-voxel variability. However, by taking the mean HU of a region, this effect is likely minimal.

Our results suggest that a correction for contrast enhancement can be used to accurately measure muscle HU values in contrast-enhanced CT scans. This has important implications for harmonizing contrast and NC muscle measures to move toward implementation of CT body composition analysis in a clinical setting by capitalizing on opportunistic medical imaging. The proposed correction can be easily implemented either directly into the medical record with imaging software or can be indirectly applied by a clinician in practice. Further research should be conducted to confirm these findings and investigate the applicability of this method for broader CT protocols and devices, other muscle groups, and other tissue types.

CONCLUSIONS

In conclusion, our study successfully validated a simple correction method for contrast enhancement in muscle measurements obtained from computed tomography (CT) scans. This study addresses a significant issue in using CT scans as an opportunistic diagnostic tool, particularly in the diagnosis of muscle wasting conditions such as sarcopenia. Once our previously determined −7.5 HU correction was applied, it resulted in muscle density measurements that were statistically equivalent to those from NC-enhanced scans. This was consistent across a novel patient population, axial muscle location, size of muscle measurement, and contrast phase. Our findings suggest that this correction method may be generalizable to novel datasets, including different locations, scanner protocols, and muscle measurements. This method is a practical tool for harmonizing data from contrast-enhanced and NC-enhanced CT scans, leading to more accurate diagnoses and improved research outcomes.

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