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**STANDARD ARTICLE**

# Use of computed tomography and radiation therapy planning software to develop a novel formula for body surface area calculation in dogs

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**Background:** Body surface area (BSA) can reflect metabolic rate that might normalize dosing of chemotherapeutics across widely variable weights within a species. The current BSA formula for dogs lacks height, length, and body condition.

**Hypothesis:** Computed tomography (CT) imaging will allow inclusion of morphometric variables in allometric modeling of BSA in dogs resulting in an improved formula for BSA estimation.

**Animals:** Forty-eight dogs from 4 institutions with whole-body CT images.

**Methods:** Retrospective and prospective case series. Body surface area was contoured using whole-body CT scans and radiation therapy planning software. Body length and height were determined from CT images and also in 9 dogs by physical measurement. Nonlinear regression was used to model the BSA data sets using allometric equations. Goodness-of-fit criteria included average relative deviation, mean standard error, Akaike information criterion, and $r^2$ (derived from the r-value generated by regression models).

**Results:** Contoured BSA differed from the current formula by −9% to +19%. Nonlinear regression on untransformed data yielded BSA = 0.0134 × body weight [kg]^0.4746 × length (cm)^0.6393 as the best-fit model. Heteroscedasticity (increasing morphometric variability with increasing BSA) was an important finding.

**Conclusions and Clinical Importance:** Computed tomography-derived BSA was used to incorporate body length into a novel BSA formula. This formula can be applied prospectively to determine whether it correlates with adverse events attributed to chemotherapy.

**KEYWORDS**

allometric, calculation, chemotherapy, metabolism, morphometry, oncology

## 1 | INTRODUCTION

Cancer chemotherapeutic drugs are often administered using an estimation of body surface area (BSA) rather than body mass. This approach

was originally adopted because BSA was believed to correlate with physiologic variables, such as blood volume and basal metabolic rate.[1,2] Additionally, the maximum tolerated doses of chemotherapeutic drugs correlated between rodents and humans when doses were normalized to BSA.[1,3] The first known formula used to estimate BSA was published in 1879, by replacing volume in the traditional surface area equation (SA = volume^{2/3}) with the weight of the subject. With this principle, the BSA of 6 adults and 10 children was measured to derive the BSA equation: BSA = (0.1053 × weight)^{2/3}.[4,5] The current equation used to estimate BSA in dogs is traditionally expressed as BSA (m^2) = (10.1 × W^{2/3})/10 000, where W is the body weight in grams (conversion to

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kg-based formula yields 0.101 × body mass (kg)$^{2/3}$, and was developed in 1911 based on data from only 6 puppies.[6,7]

Many formulae exist for BSA both within and across species, with several limitations, and these studies and limitations have been reviewed.[8] For dogs, aside from the small sample size used to develop the equation, morphometric variables were not considered in its derivation. This is potentially important, given the marked breed-associated conformational differences in dogs as compared to many other species. Therefore, the use of a single shape factor (the K factor 10.1 or 0.101 in the formula above) or the exclusion of variables meant to account for morphometric variability might not be appropriate for a given species.[8] This view is supported by BSA modeling in the guinea pig, rat, and cat wherein a nonconstant shape factor was found to improve BSA estimation.[9-11] Evidence in dogs suggests that addition of a morphometric variable (eg, length or height) might enhance the predictive utility of allometric-type BSA equations.[12] In human medicine, the Dubois equation is the most widely used for BSA estimation and includes patient height (0.20247 x height (m)$^{0.725}$ x weight (kg)$^{0.425}$).[13] In elephants, BSA is accurately estimated by single linear variables, independent of body weight.[14] The current formula for dogs lacks a measure of height, length, or proportion and does not account for physiologic variables such as body condition, age, or organ function.

In addition to the considerations noted above, questions have arisen about the appropriate use of BSA-based antineoplastic drug dosing in both animals and humans. Because most anticancer drugs have a narrow therapeutic index, minor changes in dosing can have meaningful sequelae such as decreased efficacy or increased toxicosis. Melphalan, cisplatin or carboplatin, vinblastine or vincristine, and doxorubicin toxicoses have been more frequently observed in smaller than in larger dogs.[15-20] For doxorubicin, plasma concentrations in small dogs were higher with BSA-based dosing compared to body mass-based dosing, and doxorubicin is therefore commonly administered on a per kilogram basis in dogs less than 15 kg, though the data used to support this recommendation used a cutoff of 10 kg.[21] Furthermore, in humans, there is evidence that BSA-based dosing might not be appropriate for all anticancer drugs. For example, BSA has a poor correlation with glomerular filtration rate and no correlation with liver function.[22-24] Despite these limitations, BSA-based dosing will continue to be the basis for most cytotoxic chemotherapy drugs, and an improved formula is needed for BSA estimation in the dog.

Computed tomography (CT) modeling has been used to formulate a K constant in rabbits. In that study, CT images from 12 pet rabbits were transferred to radiation therapy planning software and 1 mm slices were used to generate the surface contours to determine BSA, and nonlinear regression was then used in the current formula to generate a K constant of 9.9.[25] This was similar to another CT-based derivation of a BSA formula for ferrets which yielded a K constant of 9.94 with the help of 3D surface modeling using open-source imaging software to determine BSA.[26] These values are similar to the K constant of 10 used in cats and 10.1 used in dogs.[6,7] A slightly different approach was used in 40 laboratory miniature pigs for which CT scans and high-speed 3D software yielded the equation 100 × BSA (m$^2$) = 7.98 ×BW (kg)$^{2/3}$.[27] The authors used 5 mm slices, repeating each scan 5 times, and derived K constants for each of 4 different body mass exponents from other formulae. The final choice of equation was based on the smallest coefficient of variation.[27]

Because the current BSA formula used in dogs does not account for morphometric variability, and with the knowledge that current radiation therapy planning software has the ability to determine dimensions of anatomic compartments, we used whole-body CT to record BSA. This was measured by skin surface contouring, and morphometric variables including body length as well as surrogate measures of height. Our study objectives were to derive the best-fit formula that was produced for estimation of BSA using these variables, and use measures of conformity to describe how well the resulting formula fit the data set. We hypothesized that inclusion of morphometric variables would result in improved estimation of BSA compared to traditional body mass-only models.

## 2 | METHODS

### 2.1 | Whole-body CT scans

A total of 48 whole-body CT scans were used for which all parts of the dog were included (tip of nose to tip of tail). Of these, 39 were retrieved retrospectively and 9 were generated prospectively. All dogs were scanned for clinical reasons, in the course of evaluating clinical signs as an available diagnostic test. Any dog that had a CT scan and a recorded body weight that included the entire surface area was eligible; the reason for the CT was irrelevant. Sex (when available) and weight were recorded. Scans were assessed for positioning such that skin-to-skin contact was minimized and could be contoured in any identified crevices or skin folds. After separately contouring small parts that were sometimes missing, such as tips of toes or tips of tails, it was determined (by R. Girens and K. Selting) that minor losses (not quantified for each case but expected to be a fraction of a percent based on the cases for which it was quantified) did not impact the overall result, and thus these omissions, though rare, did not preclude using those scans. Dogs whose scans were generated prospectively had length and height measurements performed when awake in addition to collecting all the same data as the scans retrieved retrospectively. Images from these 48 dogs were obtained from the University of Missouri (MU, n = 26 including 17 retrospective and 9 prospective), the University of Florida (UF, n = 12), the University of Minnesota (UMN, n = 9), and Epigenix (n = 1). Computed tomography scanners at these institutions were a helical CT (MU, Toshiba Aquilion 64 slice; Toshiba America Medical Systems, Tustin, California), a multidetector row CT (UF, Toshiba Aquilion 8 slice; Toshiba America Medical Systems), and a PET/CT scanner (UMN, Siemens mCt-64 Biograph TrueD HD). When indicated, procedures were approved by Institutional Animal Care and Use Committees (MU ACUC protocol 8359, UMN ACUC protocols 1110A06186 and 1507-32804A), with all other scans obtained retrospectively from dogs undergoing routine care and imaging for diagnostic purposes. An additional 93 scans (UF n = 28; MU n = 14; Epigenix n = 51) were evaluated but excluded because they were missing large portions of head or extremities.

### 2.2 | Body measurements

Dogs were categorized based on weight as follows: small <10 kg, medium 10-30 kg, and large 31-45 kg. No dogs were scanned that

weighed more than 45 kg, as no dog was recruited for a whole-body scan to be used for this purpose during the study period or in the retrospective cases. Scans from dogs of any sex, breed, and age were used. Dogs assessed prospectively were evaluated by a nutritionist (M. Sprinkle) for body condition score, and subjective assessment based on CT findings (ie, amount of subcutaneous fat) was noted during contouring to ensure that no dog was excessively thin or fat. No scan was excluded because of body condition. Body condition was assessed because it could indirectly affect BSA via body mass and is an unknown variable. Not enough dogs were scored to include as covariate in the nonlinear regression, but body condition is mentioned descriptively as is the signalment.

Body measurements were obtained via CT scans. Dog length was found by measuring from the manubrium to the ischial tuberosity. Dog height was estimated using intracranial dimensions. Briefly, intracranial distance was measured from the base of the foramen magnum to the ethmoid bone to estimate shoulder height. Estimated height at the shoulder was equal to $1.016 \times D - 31.2$, where D is the internal dimension of the cranial cavity. This has been evaluated in brachycephalic, mesocephalic, and dolichocephalic dogs with square correlation coefficient ($R^2$) of 0.72, 0.84, and 0.85, respectively.[28] Prospectively, animals were measured on the same day that whole-body CT scans were obtained. Dogs were measured from manubrium to the ischial tuberosity, with the measuring tape traveling around the shoulder and thigh. Dog height was measured at the highest part of the shoulder. These measurements were compared to those derived from the same dogs on CT, and CT-derived measurements were used in regression analyses to be consistent with all other dogs in the data set. In addition, a separate group of dogs (n = 5) was measured using an external
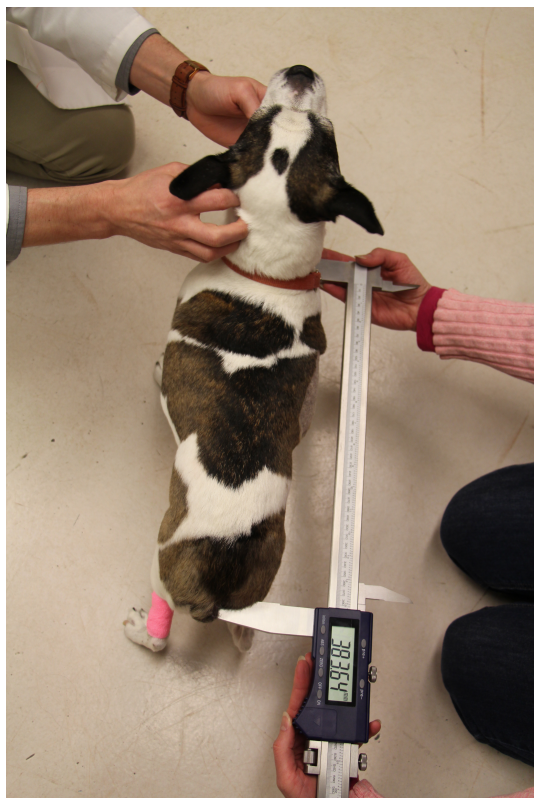


**FIGURE 1**    Calipers used to measure body length in an awake dog

1 m caliper (Machine DRO, Hertfordshire, United Kingdom; part number ME-CAL-LO-1000) from manubrium to ischium (Figure 1), and this length was compared to the corresponding length determined on CT.

## 2.3 | Body contouring

For the first 11 CT studies, images were transferred to XiO radiation treatment planning software (Release 2.6; Elekta, Stockholm, Sweden). The dog was contoured using the all-slice contouring function and then edited in each 2-D plane. A 1 mm thick virtual bolus was applied around each 2-D image to obtain the perimeter length of each slice. Images from the first dog were contoured both with 1 and 3 mm slices and resulting BSA were compared. Bolus lengths were then added together and multiplied by 0.1 or 0.3 cm (depending on slice thickness) to transform length into area. The result was divided by 10 000 to convert from $cm^2$ to $m^2$. There was no appreciable difference between results obtained from 1 vs 3 mm thick slices (0.522 vs 0.521, 0.2% difference), and all subsequent CT studies were calculated using 3 mm thickness. Though only 1 study was used to compare 1 vs 3 mm slice thickness, the use of 3 mm slices for all studies was considered rational based on the relative size of the slice to any size dog and also allowed inclusion of more scans. The first 11 cases that were evaluated on XiO were repeated, and all 37 subsequent studies analyzed, using RayStation treatment planning software (Release 4.7; RaySearch Laboratories, Stockholm, Sweden). Dogs were contoured using the gray scale threshold function (−250 to 1000 HU), then edited in each 2-D plane to remove irrelevant contours such as the table, anesthesia equipment, and air in crevices. Inner and outer walls were then applied 0.1 mm in each direction. The volume of each wall was then transformed into an area using the equation ([volume/0.1 mm]/10 000) to convert to $m^2$. The inner and outer wall areas were then averaged to obtain BSA.

## 2.4 | Determination of accuracy and precision

To assess the accuracy of using CT images with radiation therapy planning software to determine BSA, a geometric shape with a known surface area was scanned and contoured using the CT scanner at MU. To evaluate contouring precision, 1 dog (from Epigenix) was evaluated with serial whole-body CT scans by a single observer (R. Girens). Of 4 available scans, 3 were of good quality and represented serial time points at which the dog's body weight was consistent; each was contoured to determine BSA. An additional step to ensure accurate information from CT imaging involved comparing body weight in kilograms (as recorded in the medical record and collected from weighing on a hospital scale) to the CT volume in cubic centimeters (which is expected to be equivalent to kilograms when converted to liters), as these 2 measures should be equal.[29]

## 2.5 | Interobserver variation

Contouring for all 48 dogs was performed by a single investigator (R. Girens) for consistency. In addition, to assess the possible influence of interobserver variation, 2 investigators (R. Girens and C. Maitz) independently (blinded to each other's findings) evaluated a subset of 9 randomly selected CT studies using RayStation to determine BSA,

3 in each of the weight categories. Interobserver variability was quantified using Bland-Altman analysis combined with Pearson's linear and Spearman's rank correlation coefficients.

## 2.6 | Nonlinear regression

Data analysis was performed with Matlab (version 2016b) using custom written scripts and built-in functionality from the Statistics and Machine Learning Toolbox (version 11.0; Matlab is a product of Math-Works [www.mathworks.com, Natick, Massachusetts]). Least-squares nonlinear regression was performed using the fitnlm function based on the Levenberg-Marquardt algorithm. Approximate linearized 95% confidence intervals for variables were produced using the nlparci function. The model building and assessment process was based on previously published allometric-type structural models from the veterinary literature using a variety of assumptions on the structural model errors including constant errors, proportional errors, and weighting schemes.[8,26] In addition, related models using various combinations of the available predictor variables (ie, body mass, height, and length, as well as various combinations and ratios of height and length) were also investigated. Parameter constraints and data transformation techniques were not utilized—all regressions were performed on untransformed data.[30,31] Regression results were examined using visual inspection of predicted responses plotted together with measured values, residual plots, residual histograms, and normal probability plots of residuals.[32–35] Additionally, Spearman's correlation coefficient for weighted studentized residuals against predicted values was used to aid detection of residual heteroscedasticity (unequal variability of BSA across the range of predictor variables).[35] Although extreme values were generally retained, these tools were similarly used to identify potential outliers in the data set for exclusion from the final analysis. Regression diagnostics such as Cook's distances and leverage values were also utilized to aid identification of outliers. The optimal model was selected based on visual inspection of regression curves, the Akaike information criterion (AIC), mean squared errors, and r-squared values.[33–35] The AIC balances goodness of fit with simplicity of the model. In the case of nested models, these criteria were supplemented by conducting $F$ tests to help determine whether the greater flexibility provided by more variables resulted in a statistically improved fit (significance was set at $P < .05$).[32]

## 2.7 | Goodness of fit

We chose 4 methods of model discrimination statistics: average relative deviation (ARD), mean standard error (MSE), AIC, and $r^2$ (derived from the r-value generated by regression models). The ARD is defined as $(1/N) \times SUM(abs[predicted-measured]/measured)$.

## 3 | RESULTS

### 3.1 | Subjects

Dogs assessed prospectively were of adequate body condition (assessed by 1 investigator, MS, and all were at least 3 out of 9); based on CT findings of all dogs, none was noted to be excessively thin or fat. From

available data of the 48 dogs assessed, the age range was 4 months to 15 years (median 9 years), and the body weight ranged from 3.6 to 44.2 kg (median 23.5 kg). There were 24 females (spayed n = 15, intact n = 3, unknown n = 6) and 24 castrated males. Thirty-six purebred dogs and 12 mixed-breed dogs were included; Chihuahua (n = 2), Maltese (n = 1), Miniature Pinscher (n = 1), Dachshund (n = 2), Miniature Poodle (n = 1), West Highland Terrier (n = 1), Pomeranian (n = 1), Lhasa Apso (n = 1), Yorkshire Terrier (n = 1), Jack Russell Terrier (n = 1), Akita (n = 1), Welsh Corgi (n = 1), Beagle (n = 2), Labrador Retriever (n = 4), Alaskan Malamute (n = 1), Greyhound (n = 1), Basset Hound (n = 1), Vizsla (n = 1), Airedale Terrier (n = 1), Border Collie (n = 1), Golden Retriever (n = 2), Goldendoodle (n = 2), German Shepherd (n = 2), Rhodesian Ridgeback (n = 1), Doberman Pinscher (n = 1), Rottweiler (n = 1), and Newfoundland (n = 1).

### 3.2 | Accuracy and precision

The 50 cm cube has a surface area of 15 000 cm$^2$ and CT images contoured using Raystation yielded 14 992 cm$^2$, a difference of 0.05%. In addition, the volume of this cube is 125 000 cm$^3$ and the volume on Raystation was 126 217 cm$^3$ (<1% difference). Also, there was no significant difference among dogs between CT-estimated weight based on contoured volume, and body weight per hospital scale ($P = .48$). Serial scans on the same dog on different dates yielded weight and corresponding CT-based BSA of 6.02 kg and 0.332 m$^2$, 6.09 kg and 0.319 m$^2$, and 5.7 kg and 0.308 m$^2$, respectively. These were 0%-5% different from the corresponding calculated BSA, and the first 2 values which were almost identical had BSAs that were 4% different from each other. There was no significant difference in BSA for the 11 studies contoured by both planning systems when comparing XiO to Raystation results ($P = .31$ by student's $t$ test).

### 3.3 | Interobserver variation

Pearson's linear (rho = 0.9995) and Spearman's rank (rho = 1.0000) correlation coefficients found that the coefficients were statistically different from 0 ($P < .001$), and Bland-Altman analysis confirmed robust agreement between observers (Bias ± LOA: 0.006003 ± 0.029949 m$^2$) with inconsistent bias (worst case bias 0.036) and greater variation with large dogs. Though statistically significant for large dogs (per correlation coefficients), the clinical relevance is questionable (median 0.8188 for observer 1 versus 0.8262 for observer 2). This would result in a difference of less than 1% in drug dose for commonly used cancer chemotherapeutics. This is further illustrated in Figure 2 with linear regression.

### 3.4 | Derivation of a best-fit equation for BSA

Computed tomography-derived BSA data as a function of body mass are given in Figure 3 for the 48 subjects included in the study (circles). Diagnostic plots of subject length and height versus BSA are given in Figure 4A and B, respectively. Because a large number of candidate structural models were investigated, here we present only the overall best-fit model but also include the best-fit body mass-only allometric model for comparison. In both cases, a single observation (Figure 3,
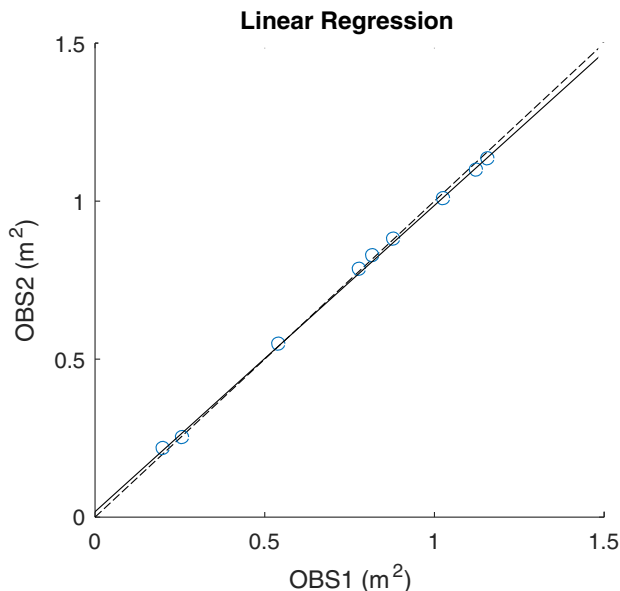
**FIGURE 2** Linear regression shows agreement between 2 blinded observers and values were not statistically different across 3 randomly selected studies in each of the 3 weight groups (9 dogs total)

dark circle) was found to be an outlier and was excluded from the final analyses. These structural models, their variables with linearized 95% confidence intervals, and their regression statistics are given in Table 1. Because these models are nested, an $F$ test was performed and gave $P < .001$ indicating rejection of the null hypothesis that the
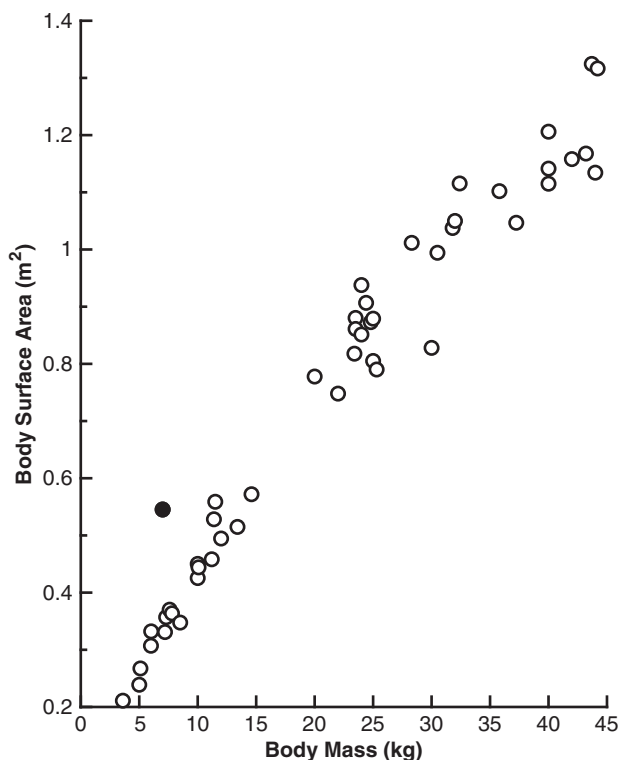


**FIGURE 3** Computed tomography-derived body surface area as a function of body mass in 48 dogs (clear circles). The single filled circle represents a statistical outlier identified during the nonlinear regression modeling process and was excluded from the final data analysis
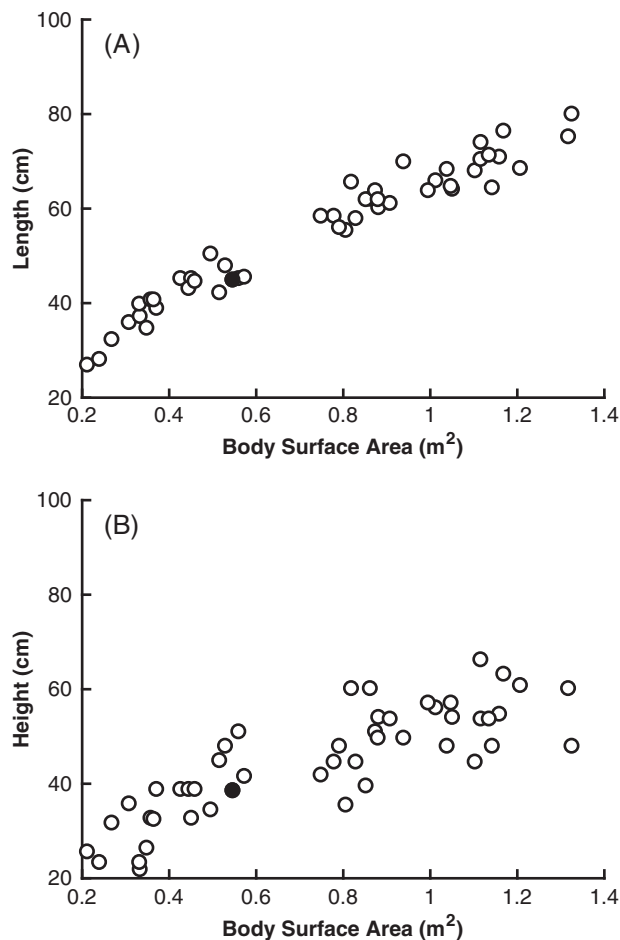


**FIGURE 4** Length (A) and height (B) as a function of computed tomography-derived body surface area in 48 dogs. The single filled circle in each plot represents a statistical outlier identified during the nonlinear regression modeling process and was excluded from the final data analysis

reduced (ie, body mass-only) structural model was superior. For both structural models, a proportional error model was found to be superior to other error models in terms of correcting residual heteroscedasticity. Weighted raw residuals are plotted against predicted values in Figure 5 illustrating a lack of evidence for heteroscedasticity with this error model choice. Finally, for the best-fit body-mass only model, Figure 6 shows the raw data as a function of body mass together with the final regression curve and 2 additional curves corresponding to the same structural model with the $B$ parameter set to its lower and upper linearized confidence interval bounds to provide an intuitive understanding of the influence of this parameter on the predictions. Similar results are not presented for the overall best-fit model due to difficulties with visualization of the associated prediction surfaces. Final measures of goodness of fit were ARD 0.0399, MSE 0.0025, AIC −185.5 (the more negative the number, the better the fit), and $r^2 = 0.99$.

When comparing clinically achievable methods of determining body length to CT measurements, a tape measure passed around the hip and shoulder (manubrium to ischium) was a mean of 13% (SD 0.05) longer than the CT measurement. Therefore, when using this method, the result should be decreased by 13% before including length in the

**TABLE 1** Parameter values with linearized 95% confidence intervals and regression statistics for the overall best-fit (column 3) and best-fit body mass-only (column 4) structural models determined from nonlinear regression of untransformed CT-derived body surface area (BSA) measurements to available independent variables [i.e. body mass in kg (W), length in cm (L), and height in cm] in 47 dogs

| | Model (BSA measured in $m^2$) | |
| --- | --- | --- |
| | $BSA = A \cdot W^B \cdot L^C$ | $BSA = A \cdot W^B$ |
| Parameter | | |
| A | 0.0134 (0.0052-0.0216) | 0.0847 (0.0777-0.0917) |
| B | 0.475 (0.392-0.557) | 0.717 (0.689-0.745) |
| C | 0.639 (0.429-0.850) | N/A |
| Regression statistic | | |
| MSE ($m^4$) | 0.0025 | 0.0045 |
| $r^2$ (adjusted) | 0.9902 | 0.9821 |
| AIC | −185.5 | −158.1 |
| ARD | 0.0399 | 0.054 |

For parameter values, confidence intervals are given in parentheses. Abbreviations: AIC, Akaike information criterion; ARD, average relative deviation; BSA, body surface area; MSE, mean squared error.

resulting equation. Measurement with an external caliper was within 10% (with most subjects within 2%) of the CT value and can be used directly in the resulting equation (data not shown).
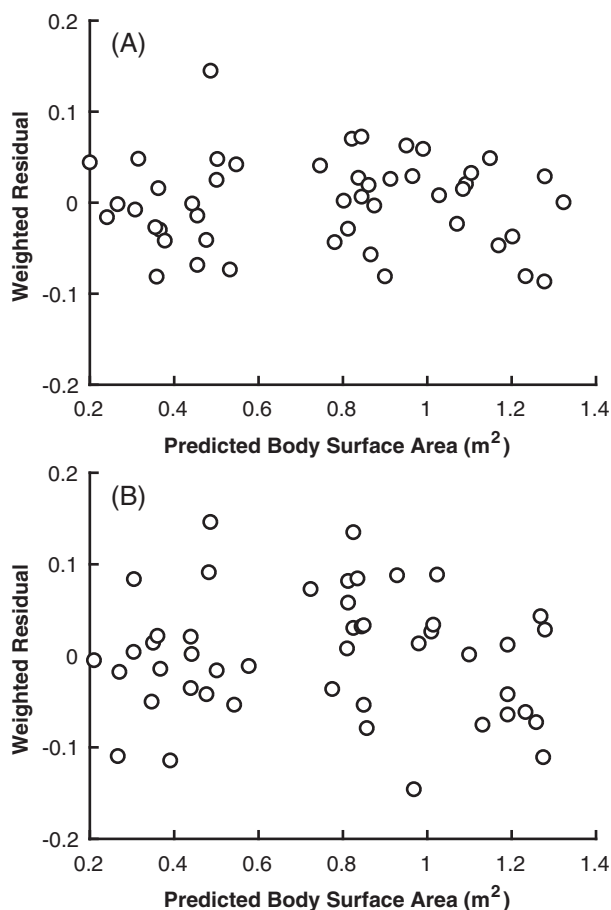


**FIGURE 5** Weighted raw residuals for the overall best-fit (A) and best-fit body mass-only (B) structural models as a function of predicted body surface area (BSA) in 47 dogs. In both cases, a proportional error model was used
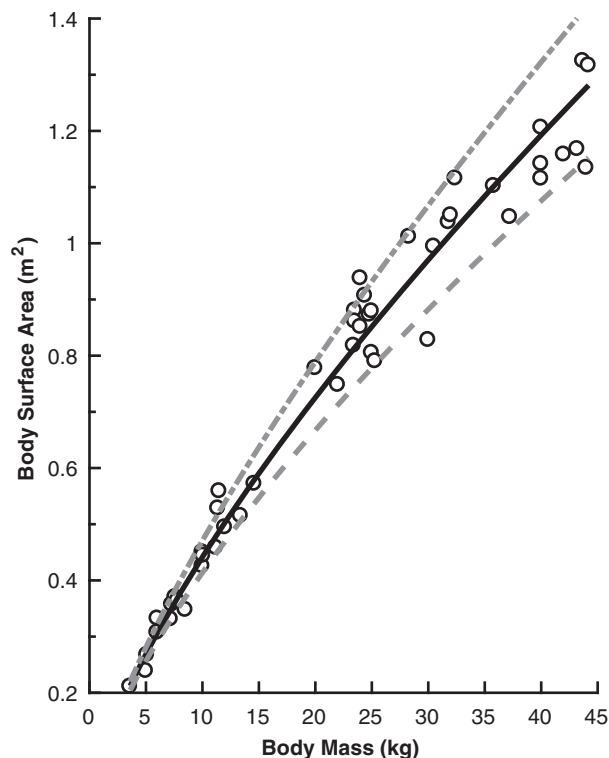


**FIGURE 6** Nonlinear regression best-fit body mass-only structural model predictions (solid bold curve) plotted with computed tomography-derived body surface area (BSA) measurements (open circles) in 47 dogs. The gray dashed and dot-dashed curves represent predicted BSA when the B parameter takes its lower (B = 0.689) and upper (B = 0.745) linearized 95% confidence interval bounds, respectively

## 4 | DISCUSSION

Here we investigate a possible method of optimally calculating an estimated BSA using a data set of 48 dogs. The equation derived from CT data (Figure 7) demonstrated excellent performance based on 4 different regression statistics. Interestingly, the addition of length did improve the derived equation though only marginally. Comparing this method to the current formula or to corresponding charts, the current formula underestimated or overestimated BSA (up to 19%).

There are limitations to consider with these data. The weight divisions were arbitrary, and it is relevant to note that increasing weight was associated with increased BSA variability. An additional limitation is that all measurements were performed once, as opposed to using multiple observers and calculating an average result. Although this provided consistency in those measurements, it is also possible that variation among observers could yield different findings. This was addressed in a small subset of dogs (n = 9) in our study, and no clinically relevant difference was found. It is worth noting that even this smaller subset of dogs constitutes more dogs than were used to generate the original

$$BSA = 0.0134 \times W_{(kg)}^{0.4746} \times L_{(cm)}^{0.6393}$$

**FIGURE 7** Final equation for calculating body surface area, derived from computed tomography data

BSA formula that is in widespread use today. Length was determined using CT which would not be reasonable to perform on every dog receiving chemotherapy for the purpose of drug dosing. To address this, we found that the use of an external caliper provided readily obtainable measurements that accurately reflected those used in the regression modeling. Additionally, though weight can fluctuate throughout a course of chemotherapy over time, the body length should not change and repeat measurement of length should not be needed for each dose. Table 2 shows selected dogs' length and weight by breed to illustrate anticipated differences between the proposed (new) and current (old) formula. Limitations of data acquisition also include the possible effect of variable body positions on measured data. For example, body length could be affected by the degree to which a dog is stretched or contracted when positioned. Also, skin folds and crevices can be difficult to contour. The 1 dog for which serial scans were available had a difference of 4% between 2 scans of essentially the same weight. Observer variation (for editing contours) and positioning are 2 possible explanations for this observation. Subjective visual inspection of scans found similar positioning, but subtle differences could have contributed to the difference.

There are also limitations to consider regarding the derivation of the equation. Although aided by various diagnostics, selection of a superior structural model in nonlinear regression is associated with an inescapable subjectivity. For example, the F test for comparing nested nonlinear models is only approximate and is dependent on the degree of intrinsic nonlinearity in the model.[35] This limitation was addressed by using many different indicators of fit quality. Another limitation is that linearized confidence intervals in nonlinear regression are by definition approximations. The acceptability of such approximations is dependent upon the degree of nonlinearity as quantified by intrinsic and parameter effects curvatures.[33] However, though linearized predictions are necessarily approximations, the nonlinearity of allometric type models is not anticipated to be of large magnitude. Regarding regression, it is important to remember that it does not constitute a method for proving the correctness of a model beyond relative comparisons to the performance of other models for a given data set.

**TABLE 2** Hypothetical cases by breed are noted with estimated length and weight taken from subjects in the data set to illustrate the impact of an improved formula

| Weight (kg) | Breed | Length (cm) | BSA (old) | BSA (new) |
|---|---|---|---|---|
| 5 | Chihuahua | 28.2 | 0.296 | 0.243 |
| 10 | Lhasa Apso | 45.3 | 0.470 | 0.458 |
| 15 | Beagle | 45.6 | 0.616 | 0.557 |
| 20 | Mixed breed | 58.5 | 0.747 | 0.749 |
| 24 | Greyhound | 70 | 0.843 | 0.916 |
| 24 | Bassett Hound | 62 | 0.843 | 0.847 |
| 30 | Border Collie | 58 | 0.979 | 0.903 |
| 35 | Goldendoodle | 68.1 | 1.084 | 1.076 |
| 40 | Golden Retriever | 70.5 | 1.185 | 1.172 |
| 40 | Labrador Retriever | 64.5 | 1.185 | 1.107 |
| 44 | Rottweiler | 71.4 | 1.263 | 1.236 |
| 44 | Newfoundland | 75.3 | 1.263 | 1.279 |

Abbreviation: BSA, body surface area.

Past investigations demonstrated inconsistent correlation between dose and toxicity based on body size, with small dogs experiencing more toxicity and leaving a concern that larger dogs might be underdosed. In our data set, variability in BSA correlation increased with weight. This could be associated with more discrepant shapes of larger dogs (ie, the difference between a Basset Hound and a Golden Retriever of the same weight is more variable than the difference between a Pomeranian and a Shih Tzu of the same weight). Future studies should attempt to quantify this variability, consider the contribution of breed, and include dogs greater than 45 kg. The data set presented here was not sufficiently large to include breed as a covariate, and dogs greater than 45 kg were not presented within the study period nor identified retrospectively. Quantification of BSA variance would be aided by obtaining replicated data at evenly distributed body masses as this would aid the robustness of the nonlinear regression methods. For the CT-derived data presented here, we achieved good correction of the heteroscedasticity using a proportional weighting scheme.

All these information assumes that BSA is an accurate method of calculating drug dose because it might relate to organ function and thus metabolism and excretion of drugs. It is possible, and perhaps likely, that pharmacokinetics and pharmacodynamics (and thus toxicity and efficacy) are more dependent on physiologic processes such as enzyme activity as characterized by pharmacogenomics. Body composition, including fat content and muscle mass, might also impact drug distribution, especially with lipophilic drugs. In daily clinical practice, it is often impractical to use therapeutic drug monitoring or specialized testing to quantify organ function for dosing of cancer chemotherapeutics. Therefore, simple calculations using body mass alone or translating body mass with or without shape variables will continue to be the baseline from which animals are dosed, with adjustments based on tolerability of the initial dose of a given drug. A more accurate BSA equation will provide a more consistent starting point for drug dosing and toxicity assessment and could increase drug efficacy and decrease life-threatening sequelae associated with cancer chemotherapeutic drugs. This also could allow for more uniform dosing without the need to dose small dogs differently. The equations derived here should be applied in a prospective trial to determine whether a more accurate formula results in fewer adverse events from drugs that are dosed based on BSA.

## CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

## OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

## INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

MU ACUC protocol 8359, UMN ACUC protocols 1110A06186 and 1507-32804A, UF cases were all clinical cases collected retrospectively and thus were not performed under an ACUC protocol.

## HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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