An Evaluation of Tibia-Level Predictors of Fracture Characteristics in Human Tibiae

Undergraduate Research Thesis

Presented in partial fulfillment of the requirements for graduation with Research Distinction in Anthropological Sciences in the undergraduate colleges of The Ohio State University

By

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Abstract

Tibia fracture incidence accounts for over 36% of long bone fractures in adults across loading mechanisms. Additionally, the tibia is the most commonly fractured lower extremity bone in pedestrian-motor vehicle impacts. Increased fracture severity, especially in the tibia, causes increases in both the physical and financial burden associated with recovery. Current research encompasses quantification of cross-sectional tibia features, trends of these features across ages and between sexes, and how tibia features are related to fracture risk. Research is lacking, however, in identification of predictors of differences in fracture severity and identification of populations at risk for increased tibia fracture severity. Therefore, the objective of this study was to investigate relationships between individual-level and tibia-level variables with fracture severity, specifically, the number of fractures per tibia. Sixteen human tibiae (8 male, 8 female) were loaded to failure in a 4-point bending scenario at 6 m/s in a lateral-medial direction. Prior to testing, computed tomography (CT) scans of each tibia were obtained and tibia-level variables (cortical area, cortical thickness, percent cortical area, total area, endosteal area, and volumetric bone mineral density) were collected at the 50% site of each tibia. Relationships between individual-level and tibia-level variables and number of fractures per tibia were explored; however, no significant relationships were observed. General trends observed included fewer fracture numbers in females, likely influenced by smaller

tibiae and thus smaller ratios of cortical area when compared to male tibiae. Male tibiae facilitated more fractures in this study, as the more robust nature of male tibiae allowed for propagation into multiple fractures when traumatic force was applied. Future research should include a larger sample size, as well as expanded tibia-level and fracture-level variables to further investigate populations at risk for increased fracture severity.

Dedication

This thesis is dedicated to my friends, family, and academic community that supported my research efforts throughout the development of this thesis and throughout my undergraduate career.

Acknowledgments

I would like to acknowledge the anatomical donors for their gifts to the Ohio State Body Donation Program. Without these donors, the research conducted in this study, and all research conducted in the Injury Biomechanics Research Center (IBRC), would not have been possible.

I would like to thank my mentors and committee members, Drs. Angela L. Harden, Mary E. Cole, and Randee L. Hunter, for advising me. With their leadership and guidance, I have grown both academically and professionally and feel adequately prepared and excited for what the future holds with my graduate school endeavors. I am forever grateful for the opportunities they have given me and for their continued support throughout my undergraduate research career in the IBRC.

Finally, I would like to thank the students, staff, and faculty in the IBRC for continuously challenging me to explore new research endeavors and to continue learning every day. I could not have completed this project without such an amazing community of peers and mentors supporting me and pushing me to achieve my goals. The IBRC community is not only defined by outstanding interdisciplinary research, but also by a truly gifted group of researchers fostering a welcoming learning environment. I am continuously grateful for the time I have spent in the IBRC and for the friends that I have made along the way.

Vita

2019……. Beavercreek High School

Publications

Cole ME, Agnew AM, **McAdow S**, Goldsmith C, Harden AL. Preliminary Investigation of Relationships between Cortical Porosity and Fracture Type in Human Tibiae. Proceedings of the 75th Annual Meeting of the American Academy of Forensic Sciences (AAFS). (Feb, 2023): Vol. 29: 108. Poster presentation at the AAFS annual meeting; Orlando, FL, USA.

Fields of Study

Major Field: Anthropological Sciences

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Introduction

Tibia fractures account for over 36% of long bone fractures in adults across loading mechanisms[3,4]. The tibia, the medial bone in the leg parallel with the fibula, is the most commonly fractured bone in the lower extremity in pedestrian impacts (i.e., pedestrian struck by a motor vehicle)[1]. In addition to motor vehicle crashes, the tibia is frequently fractured in sports-related injuries, motorcycle crashes, and various other high-speed activities[1,2]. Tibia fracture prevalence changes between sexes with age[4,5,6]. Among younger individuals, males have a higher prevalence of tibia fractures when compared to females[4,5]. This difference can be attributed to the higher average number of males participating in intense contact sports and driving motorcycles[5]. As age increases, female tibia fracture incidence increases to surpass male tibia fracture incidence[4,5]. Fractures occurring in older populations are more likely attributed to bone fragility and falling[4].

The severity of fractures, specifically in the tibia, not only causes an increase in the healing time and the financial burden, both at the individual level and the hospital level, but also negatively affects mobility and mortality[6,8,9]. The tibia has poor soft tissue protection and blood supply, meaning the healing process is long and difficult after a fracture occurs[8,9]. Tibia fractures prevent weight bearing activities and cause both short-term and long-term pain and instability, which negatively affects mobility[6,9]. In addition to mobility limitations and ongoing pain following injury, Connelly et al. reported a high

incidence of death within one year following tibia fracture[6]. The limited mobility, long healing process, and increased mortality associated with tibia fractures not only affects the quality of life for the individual but adds a financial burden as well. The cost of hospital care, especially if surgery is required due to severe fracture, is profound. Tibia shaft fractures have a high rate of nonunion, meaning that the fracture will not heal over a long period of time[22]. Failure of healing in a timely fashion increases hospital costs per individual, with one report stating that the median cost for nonunion tibia fracture repair was over $25,000 per individual[22]. In addition to hospital care, around 20% of people that were not able to return to work following injury reportedly did not return due to continuing disability, further contributing to the financial burden of severe tibia fracture[6,10]. The economic, social, and physical burdens of severe tibia fractures make identifying populations at risk for increased injury severity in the tibia specifically a research need.

Research investigating variables contributing to increased fracture severity is limited. The current paradigm encompasses quantification of architectural aspects of tibiae (e.g., dimensional measurements like cortical thickness and cortical area), trends of these features in relationship to individual-level variables (e.g., age and sex), and how these features and their individual-level trends can be used to predict fracture risk. An investigation completed by Ruff and Hayes examined sex differences associated with age-related bone remodeling of the lower limb bones, specifically the femur and tibia[11]. In order to examine sex and age-related differences in cross-sectional geometry (e.g., total area, cortical area, endosteal area), 99 tibiae and 103 femora were collected from

embalmed autopsy donors. Several sites from the tibia (20%, 35%, 50%, 65%, 80%) and femur (20%, 35%, 5% intervals from 50-80%, mid-neck) were sampled, histologically prepared, and analyzed using image analysis software[11]. It was concluded that both men and women undergo endosteal expansion, or an age-related change in bone involving the removal of bone from the endosteal border, thus expanding the medullary cavity and decreasing the thickness of the cortical bone present[11]. Additionally, it was found that cortical area, or the dense bone layer surrounding the medullary cavity, decreases with age, but the changes are more extreme in women[11]. These changes are associated with decreases in bone strength and increases in fracture risk, which may explain the higher fracture incidence observed in older women in comparison to older men[11]. Increased bone fragility in females versus males is due to hormonal shifts during menopause, which are associated with increased porosity and lowered bone mineral density (BMD)[7]. Osteoporosis, defined as an age-associated disorder of bone remodeling that causes an increase in porosity and a reduction of cortical bone area, is associated with increased skeletal fragility and heightened fracture risk[4,7]. The majority of osteoporosis cases are elderly women, as studies have shown that women lose more bone relative to their original bone area than men do with age, and this bone loss is associated with increased fracture risk[7]. Previous research has identified cross-sectional differences across ages and between sexes and has addressed these differences' association with fracture risk. Based on previous studies, it is expected that, with increasing age, both males and females will exhibit decreases in cortical thickness, cortical area, and BMD and an increase in

endosteal area when tibia-level variables are quantified[4,7,11]. Females are expected to experience these effects to a greater degree than males[7].

An investigation conducted by Harden et al. examined relationships between age, sex, number of fractures, and type of fractures in human tibiae[12]. This study included sixty human tibiae, with age distribution matched between sexes, loaded to failure in a 4-point bending loading scenario at 6 m/s in a lateral-medial direction[12]. The investigation concluded that older adults were more likely to experience fewer fractures per tibia in a single loading event than younger individuals[12]. Harden et al. concluded that mineralization increasing with age, leading to older individuals with brittle bones, could explain the presence of fewer, yet more complex fractures in older individuals. The difference in bone composition in younger individuals may allow for more bending during the loading event, thus leading to less complex fracture types, such as wedge fractures[12]. Harden et al. calls for further research involving tibia-level variables (e.g., cross-sectional geometry) to more thoroughly investigate the relationships between individual-level variables, tibia-level variables, and fracture characteristics. It is expected that, based on the conclusions from Harden et al., individuals with age-related changes in tibia-level variables (lower cortical thickness, cortical area, and BMD and a higher endosteal area) will exhibit lower fracture number[4,7,11,12]. Additionally, because females tend to experience age-related changes in tibia-level variables to a more extreme degree than males, meaning females lose more cortical bone relative to their overall bone size with age than males, it is expected that older females will exhibit fewer fractures than older males. A preliminary investigation of the relationship between cortical porosity and

fracture types in human tibiae conducted by Cole et al. concluded that increased porosity, or the amount of cortical bone area that is accounted for by holes (void space) in the bone, may facilitate a more direct fracture propagation path through the bone[21]. Increased porosity is an age-related change in bone that is also demonstrated more so in females, meaning that females experience a higher % porosity with age than males. Based on conclusions reached by Cole et al., the hypothesis that older females will exhibit fewer fractures than older males is supported.

Identification of predictors of differences in fracture severity between individuals is a research need because it will allow for the classification of populations susceptible to more severe fractures, which are associated with both a decrease in the individual's quality of life and an increased financial burden. Additionally, identification of populations susceptible to increased injury severity is integral in future clinical applications of fracture prevention methods. While many studies have examined fracture risk, investigations of fracture severity and relationships with age, sex, and bone-specific variables have yet to be explored.

Therefore, the objective of this study was to examine relationships between individual-level and bone-specific variables with fracture severity, specifically, the number of fractures per tibia per loading event. This goal will be achieved by addressing the following aims:

Aim 1: Examine the relationships between individual-level variables and number of fractures.

Aim 2: Examine the relationships between tibia-level variables and number of fractures.

The outcomes of this study will help to fill the current gap in injury severity research; specifically, identifying populations at higher risk for increased injury severities in dynamic loading events resulting in tibial fractures. Identification of populations at risk for severe tibia fractures is important because of the physical and financial burden associated with increased injury severity. The outcomes of this study can be applied to future applications of fracture prevention methods by identifying target populations for future studies

Materials and Methods

Materials

Sixteen human tibiae (8 male [25–96 years, M=60.75 years], 8 female [29–97 years, M=60.63 years]) ethically acquired from postmortem human subjects (PMHS) from The Ohio State Body Donation Program were utilized for this study. The tibiae are a sub-sample of a larger on-going research project funded by the National Institute of Justice (NIJ- 2019-DU-BX-0040)[12,13]. Tibiae from males and females were selected to obtain an age-matched sample between sexes (Figure 1). Individual-level (e.g., age and sex [Table 1, Figure 1]) and tibia-level (e.g., cortical area [Table 1]) data were collected prior to experimental testing for each subject.

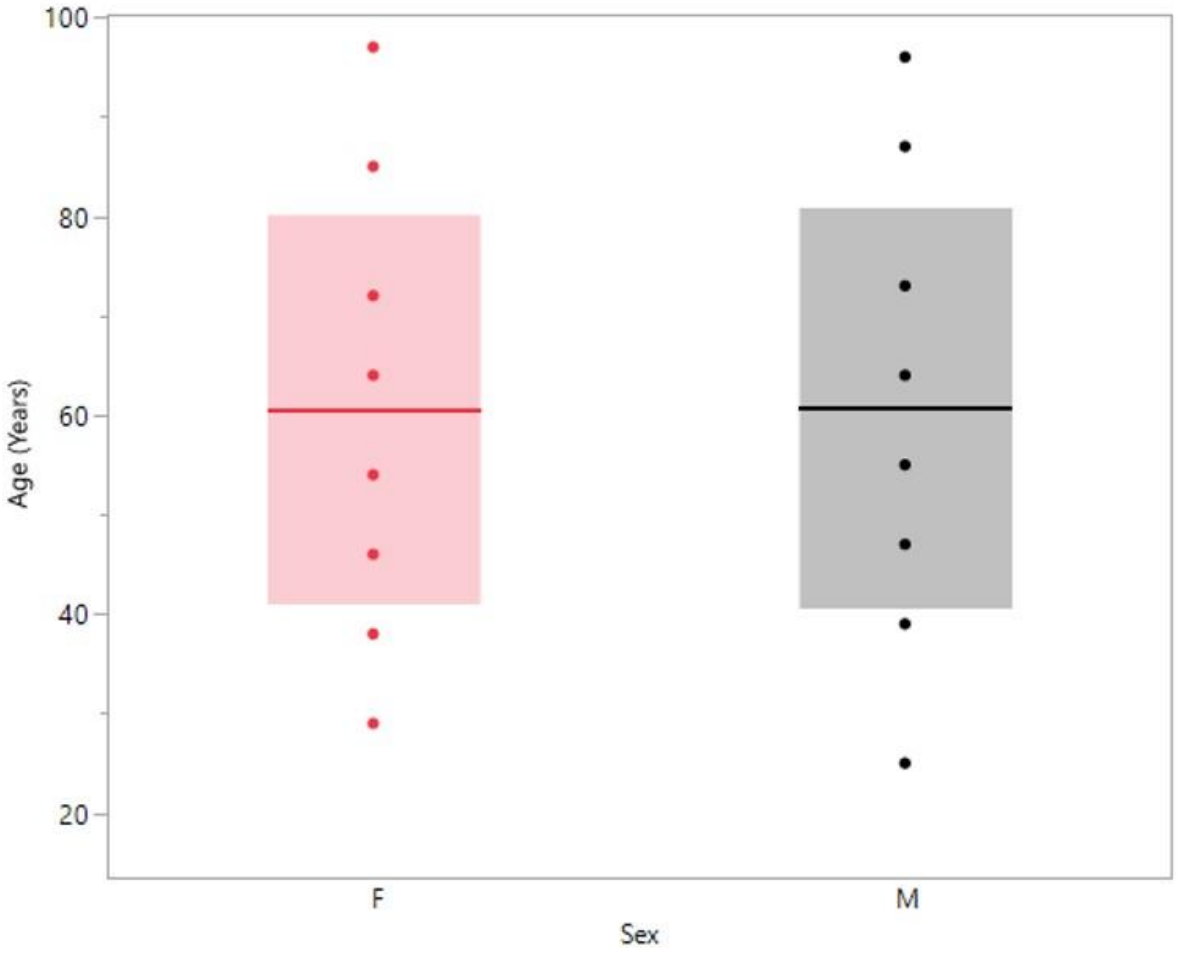

Figure 1. Boxplot of sample demographics. Females (mean=60.63) represented with red points and corresponding box and males (mean=60.75) represented with black points and corresponding box.

Pre-Test Tibia-Level Variable Quantification

Tibia-level variables were quantified prior to testing using computed tomography (CT) scans. CT scans were acquired at 0.335 mm x-y resolution using consistent acquisition parameters on a clinical CT scanner (Philips Ingenuity Vereos PET/CT). A Bone Density Calibration Phantom (BDX/6- QRM, Möhrendorf, Germany) with rods of

known calcium hydroxyapatite densities (0–800 mg/cm^3) was included as a reference in each scan to construct calibration curves for vBMD quantification. Analyses of cross-sectional parameters and vBMD were conducted using the SkyScan CTAn (Bruker) software package. Tibia length, distance from the proximal articular to distal articular surfaces (excluding the medial malleolus), was recorded for each tibia. Volumes of interest (VOIs) of ten slices spanning 6.7mm of bone length centered around the fifty-percent site for each tibia, measured as a percentage of total tibia length relative to the distal articular surface, were isolated from pre-test CT scans. The fifty-percent site was chosen for analysis in this study because this measurement represents the point in between the loading arms in the testing scenario. Six cross-sectional variables representing cortical cross-sectional geometry and volumetric bone mineral density were collected from each tibia (Table 1). To analyze cortical bone, greyscale thresholds (141-255) were consistently applied across all samples. SkyScan CTAn quantified cortical bone characteristics that represent bone mass or quantity of bone (Tt.Ar, Ct.Ar, %Ct.Ar, Ct.Th) and cortical vBMD. Es.Ar was calculated following SkyScan CTAn analysis by subtracting Ct.Ar from Tt.Ar.

Tibia Testing

All tibiae in this study were experimentally loaded to failure in a 4-point bending scenario at 6 m/s in a lateral-medial direction[12,13]. After testing, fracture characteristic data were collected by the PI of the on-going project following methods outlined in the

AO/OTA Fracture and Dislocation System[14]. Of those data, the number of fractures per tibia were included in this study (Table 1).

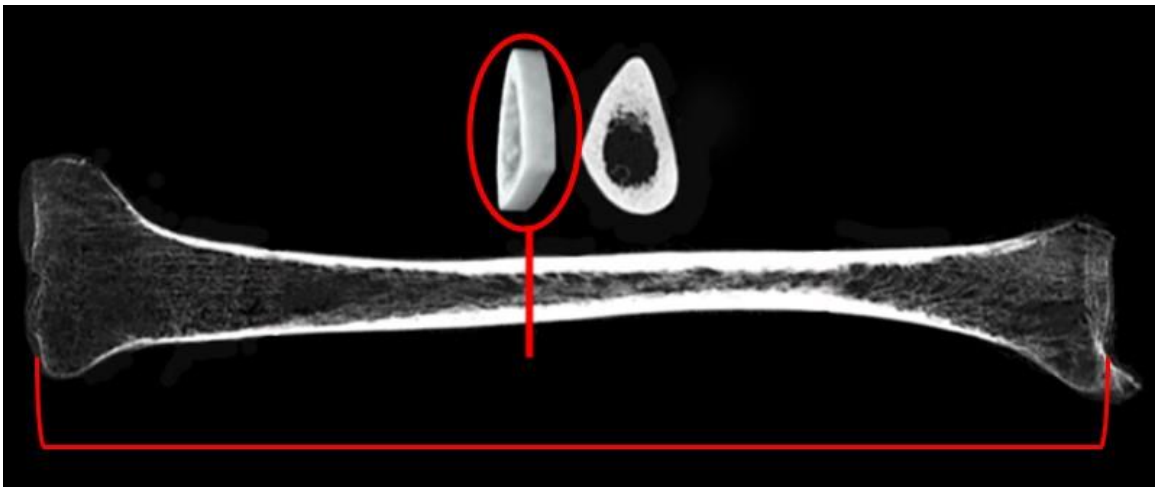

Figure 2. Tibia length diagram. Computed tomography image of a human tibia with the length margins delineated and the 50% VOI highlighted in red.

Table 1. Variable definitions. Definitions of individual, tibia-level, and fracture characteristic variables examined in this study.

Variable	Abbreviation	Unit	Definition
Individual-Level Variables			
Age	-	-	Age described as both categorical (by decade) and continuous (by year) variables
Sex	-	-	Categorized as biological male or female
Tibia-Level Variables			
Cortical Area	Ct.Ar	mm^2	All cortical bone area including pore areas
Cortical Thickness	Ct.Th	mm	Width of bone excluding the medullary cavity
Percent Cortical Area	%Ct.Ar	%	Normalized area for cross-sectional size (Ct.Ar/Tt.Ar)
Total Area	Tt.Ar	mm^2	Total area within the periosteum, including the medullary cavity
Endosteal Area	Es.Ar	mm^2	Area within the endosteum, including trabecular area and medullary area
Volumetric Bone Mineral Density	vBMD	mg/cc	Bone mineral density throughout the three-dimensional bone volume calibrated from a phantom standard
Fracture Characteristic Variables			
Number of Fractures	-	-	Number of classified fracture types in a single tibia

Statistical Analysis

Statistical analyses were conducted using JMP (Version 16.2)[15]. Descriptive statistics (mean, median, standard deviation) were assessed for all cross-sectional variables, in aggregate and with subdivisions by sex. Univariate analyses were conducted according to Table 2. Fracture number per tibia was described as "1" or "2+" in statistical analyses due to limitations of the sample size of each category. Alpha levels were set *a priori* at 0.05. Normality (Shapiro-Wilk) and homogeneity of variance (Levene's Test)

were assessed to confirm the use of a parametric t-test to identify sex differences in continuous variables. In addition to the analyses outlined in Table 2, relationships between tibia-level variables and sex (T-Test) and tibia-level variables and age (linear regression) were conducted. To visualize relationships between tibia-level variables, a Pearson correlation matrix was constructed in R from package *stats* visualized with package *ggcorrplot*[16]. Additionally, principal components analyses were generated in R with package *stats* visualized with package *factoextra*[16].

Table 2. Univariate analyses between predictor variables and the response variable.

Predictor Variables	**Response Variable**
	Fracture Number Group
Individual-Level Variables	
Age	Linear Regression
Sex	Fisher's Exact Test
Tibia-Level Variables	
Cortical Area	Nominal Logistic Regression
Cortical Thickness	
Percent Cortical Area	
Total Area	
Endosteal Area	
Volumetric Bone Mineral Density	

Results and Discussion

Descriptive statistics for age, Tt.Ar, Ct.Ar, Es.Ar, %Ct.Ar, Ct.Th, and vBMD are provided in Table 3. The number of individuals per fracture number group (1 or 2+ fractures) with subdivisions by sex are provided in Table 8. Whole-sample descriptive statistics are included, as well as subdivisions by sex. The continuous variables (age, Tt.Ar, Ct.Ar, Es.Ar, %Ct.Ar, Ct.Th, and vBMD) were checked for outliers with a quantile spread, a Huber spread, and a Cauchy spread. Robust outlier tests (Huber, Cauchy) were used in addition to a quantile spread to ensure that the small sample size was accounted for. No outliers were found; therefore, no samples were excluded from statistical analyses (Table 4). Shapiro-Wilk tests for normality were completed for the entire sample, as well as for subdivisions into male and female subsamples. All continuous variables were found to be normally distributed. Levene's tests for homogeneity of variance found that males and females had equal variances for all continuous variables. Therefore, t-tests were used to compare all continuous variables between males and females (Table 5).

Table 3. Descriptive statistics of continuous individual- and tibia-level variables.

Variable	Sex	Min	Max	Mean	Std. Dev
Individual-Level					
Age (years)	All	25.00	97.00	60.69	22.94
	Males	25.00	96.00	60.75	24.10
	Females	29.00	97.00	60.63	23.38
Tibia-Level					
Tt.Ar (mm^2)	All	330.48	562.71	437.38	73.86
	Males	407.10	562.71	496.58	50.61
	Females	330.48	427.09	378.18	33.43
Ct.Ar (mm^2)	All	181.71	392.63	304.63	57.01
	Males	288.84	392.63	345.91	33.22
	Females	181.71	340.45	263.34	44.34
Es.Ar (mm^2)	All	73.90	199.88	132.75	36.16
	Males	99.33	199.88	150.67	34.96
	Females	73.90	160.56	114.83	29.09
Ct.Ar (%)	All	53.09%	79.71%	69.66%	6.73%
	Males	61.35%	77.42%	69.87%	5.13%
	Females	53.09%	79.71%	69.44%	8.41%
Ct.Th (mm)	All	2.41	5.79	4.28	0.83
	Males	3.46	5.18	4.48	0.56
	Females	2.41	5.79	4.09	1.03
vBMD (mg/cc)	All	1070.27	1245.94	1187.03	46.51
	Males	1140.25	1237.12	1191.28	28.63
	Females	1070.27	1245.94	1182.78	61.44

Table 4. Outlier tests of continuous individual- and tibia-level variables.

Variable	Huber Center	Huber Spread	Huber Outliers	Cauchy Center	Cauchy Spread	Cauchy Outliers	Quartile Center	Quartile Spread	Quartile Outliers
Individual-Level									
Age	60.69	24.18	0.00	58.34	23.61	0.00	59.50	30.58	0.00
Tibia-Level									
Tt.Ar (mm^2)	437.38	77.86	0.00	414.53	71.40	0.00	417.10	99.08	0.00
Ct.Ar (mm^2)	304.89	59.45	0.00	307.10	61.48	0.00	303.03	60.91	0.00
Es.Ar (mm^2)	132.75	38.12	0.00	125.15	35.03	0.00	125.63	41.43	0.00
Ct.Ar (%)	69.90	6.47	0.00	69.88	4.76	0.00	70.03	6.39	0.00
Ct.Th (mm)	4.30	0.84	0.00	4.43	0.67	0.00	4.40	0.85	0.00
vBMD (mg/cc)	1188.94	44.05	0.00	1197.18	35.05	0.00	1192.16	36.87	0.00

Table 5. Tests for normality and homogeneity of variance to select test for sex differences.

Variable	Normality for Whole Sample		Normality for Males		Normality for Females		Homogeneity of Variance		Test Selected
	W	p-value	W	p-value	W	p-value	F Ratio	p-value	
Individual-Level									
Age	0.96	0.61	0.98	0.97	0.98	0.94	>0.01	0.95	T-Test
Tibia-Level									
Tt.Ar (mm^2)	0.93	0.22	0.9	0.30	0.96	0.77	1.19	0.29	T-Test
Ct.Ar (mm^2)	0.96	0.65	0.97	0.87	0.93	0.54	0.09	0.76	T-Test
Es.Ar (mm^2)	0.98	0.93	0.97	0.91	0.97	0.90	0.69	0.42	T-Test
Ct.Ar (%)	0.95	0.50	0.97	0.92	0.94	0.58	0.90	0.36	T-Test
Ct.Th (mm)	0.97	0.91	0.95	0.74	0.99	0.99	2.37	0.15	T-Test
vBMD (mg/cc)	0.91	0.12	0.96	0.77	0.89	0.23	4.27	0.06	T-Test

Individual-Level Variables as Predictors of Fracture Number

No significant relationships were observed between age and fracture number group (p=0.40) or sex and fracture number group (p=0.31) (Tables 6 and 7, Figure 3). Previous studies have shown age to have a significant relationship with fracture number[12]. Research conducted by Harden et al. reported that older adults demonstrated significantly fewer fracture numbers than younger individuals in a study examining sixty human tibiae[12]. The absence of significant associations between age and fracture number in the present study could be explained by the smaller sample size, as only two individuals per age decade were included.

Preliminary research by Harden et al. did not identify significant relationships between sex and fracture number, which aligns with the results in this study[12]. However, the present study found that single fractures were more common in females (n=6) compared to 2+ fractures (n=2). In contrast, more males exhibited 2+ fractures (n=5) than one fracture (n=3) (Table 8). This difference in number of fractures, and thus fracture severity, between males and females may be attributed to tibia size differences between sexes and will be discussed in tandem with tibia-level variable results. Future studies should include a larger sample size to further examine potential sex differences in fracture number and, therefore, fracture severity.

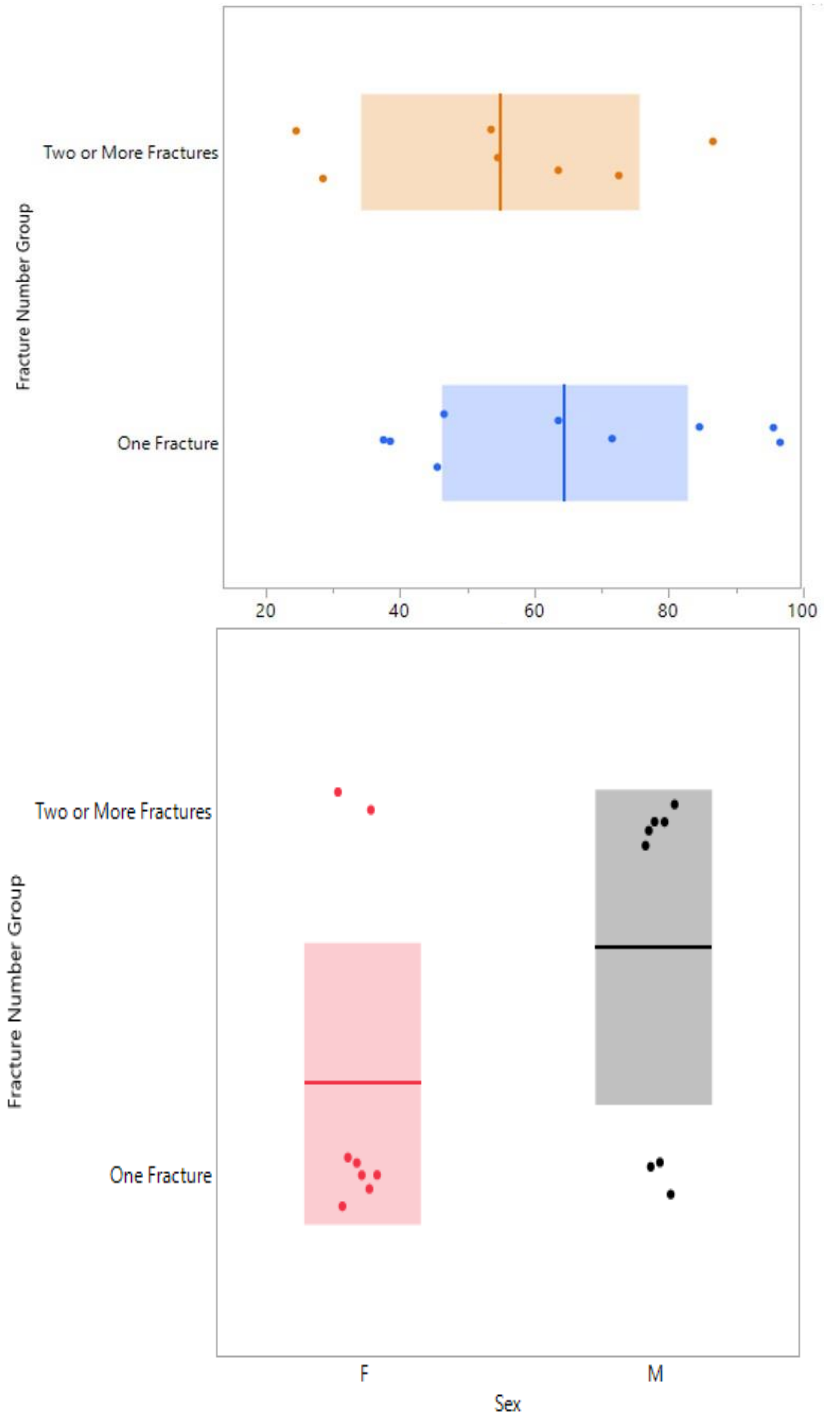

Figure 3. Boxplots of fracture number group with age (top) and sex (bottom).

Table 6. Ordinal logistic regression. Assessment of relationships between age and fracture number group.

Variable	Estimate	Std Error	Chi Square	p-value	R^2	Lack of Fit Chi Square	Lack of Fit p-value
(Intercept)	0.96	1.51	0.40	0.52			
Age	-0.02	0.02	0.71	0.40	3.42%	18.41	0.14

Table 7. Fisher's Exact test. Results assessing the relationship between sex and fracture number group.

Variable	DF	Fisher's Exact Test 2-Tail p-value	R^2
Fracture Number Group	1	0.31	10.71%

Table 8. Descriptive statistics for the fracture number group response variable.

Fracture Characteristic Variable			
Fracture Number Group	**Sex**	**One Fracture**	**Two or More Fractures**
	All	9	7
	Males	3	5
	Females	6	2

Sex Differences in Tibia-Level Variables

Significant sex differences were observed for Tt.Ar ($p<0.01$), Ct.Ar ($p<0.01$), and Es.Ar ($p=0.04$), as outlined in Table 9. These relationships were expected, as males are dimensionally larger overall than females[17,18]. Tt.Ar values were higher in males (mean=496.58 mm^2) than in females (mean=378.18 mm^2). Additionally, males exhibited higher Ct.Ar values (mean=345.91 mm^2) than females (mean=263.34 mm^2) and higher Es.Ar (mean=150.67 mm^2) than females (mean=114.83 mm^2). When Ct.Ar was normalized by determining the amount of cortical bone relative to the overall size of the

tibia, or the calculation of %Ct.Ar, there was no longer a significant difference (p=0.90) between males (mean=69.87%) and females (mean=69.44%) (Table 3). Previous studies have shown that, along with other morphometric traits (Tt.Ar, Ct.Ar, Es.Ar) males also significantly exceed females in cortical thickness[18]. This result was not found in this study, as males had a slightly higher Ct.Th (mean=4.48 mm) than females (mean=4.09 mm), but this difference was not significant (p=0.37). The lack of significance could be attributed to the small sample size utilized in this study, as demonstrated by the relatively low power for the t-test of Ct.Th (power=14.11%). Finally, previous studies have shown significantly higher cortical vBMD values in males[20]. In this study, vBMD did not differ significantly between males (mean=1191.28 mg/cc) and females (mean=1182.78 mg/cc) (p=0.73). The lack of significance could also be attributed to the small sample size utilized in this study, as demonstrated by the relatively low power for the t-test of vBMD (power=6.26%).

Principal components analysis (PCA) was conducted in order to analyze the continuous variables included in this study (individual- and tibial-level variables) grouped by sex (Figure 4). The most important dimension, accounting for 51.5% of variance between sexes, is described by variables contributing to bone size (Tt.Ar, Ct.Ar, Es.Ar) (Figure 4). The second most important dimension, accounting for 34.1% of variance between sexes, includes variables that describe the fraction of cortical bone within the Tt.Ar (Ct.Th, %Ct.Ar, vBMD) (Figure 4). The clear separation of males and females further supports the finding of this study and previous studies that, relative to females, males have larger bones[17,18]. Understanding the relationship between sex and

tibia-level variables is integral to determining populations at a higher risk for increased fracture severity, as trends in tibia-level variables associated with more severe tibia fracture can then be connected to populations that display the same trends in tibia-level variables.

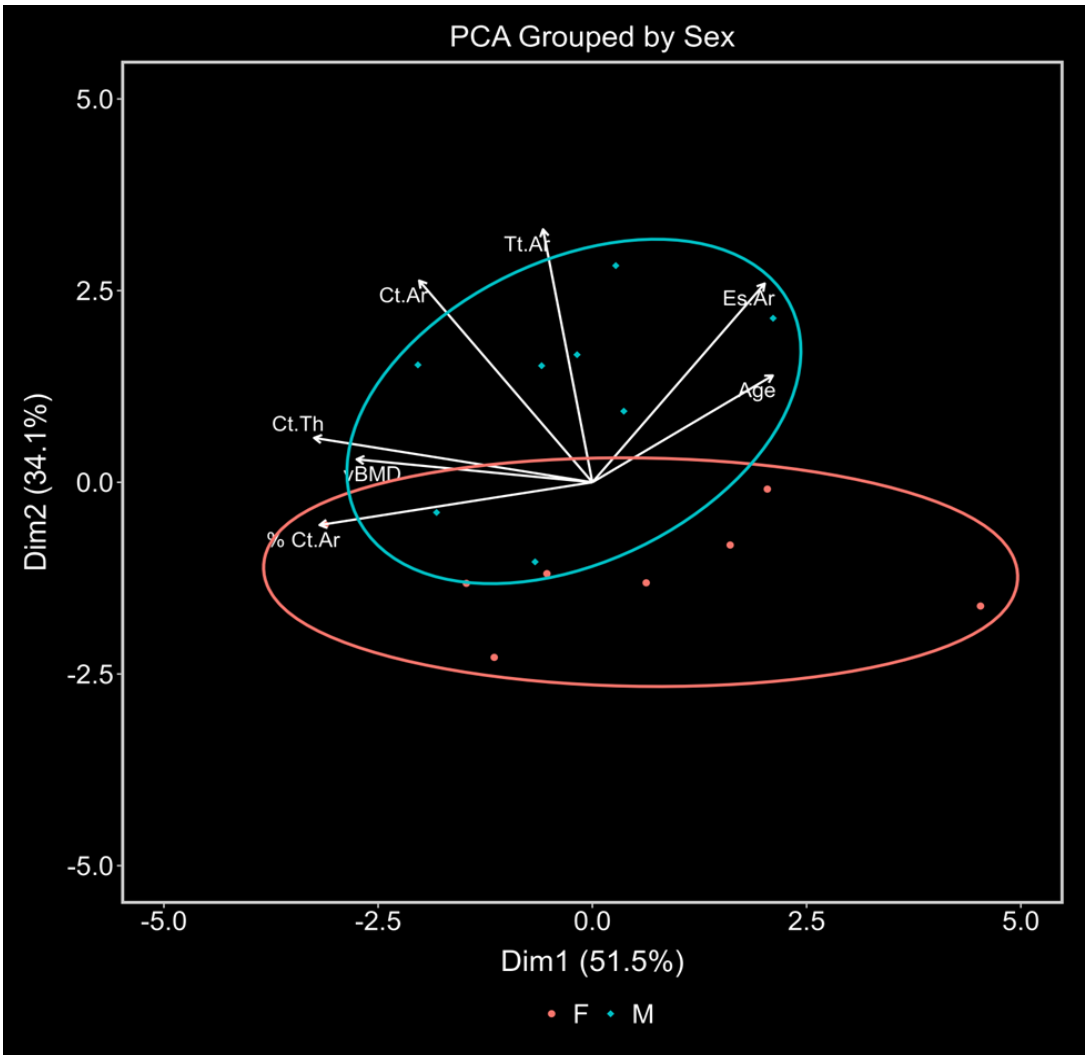

Figure 4. Principal components analysis. Analysis of continuous variables (individual- and tibial-level variables) grouped by sex.

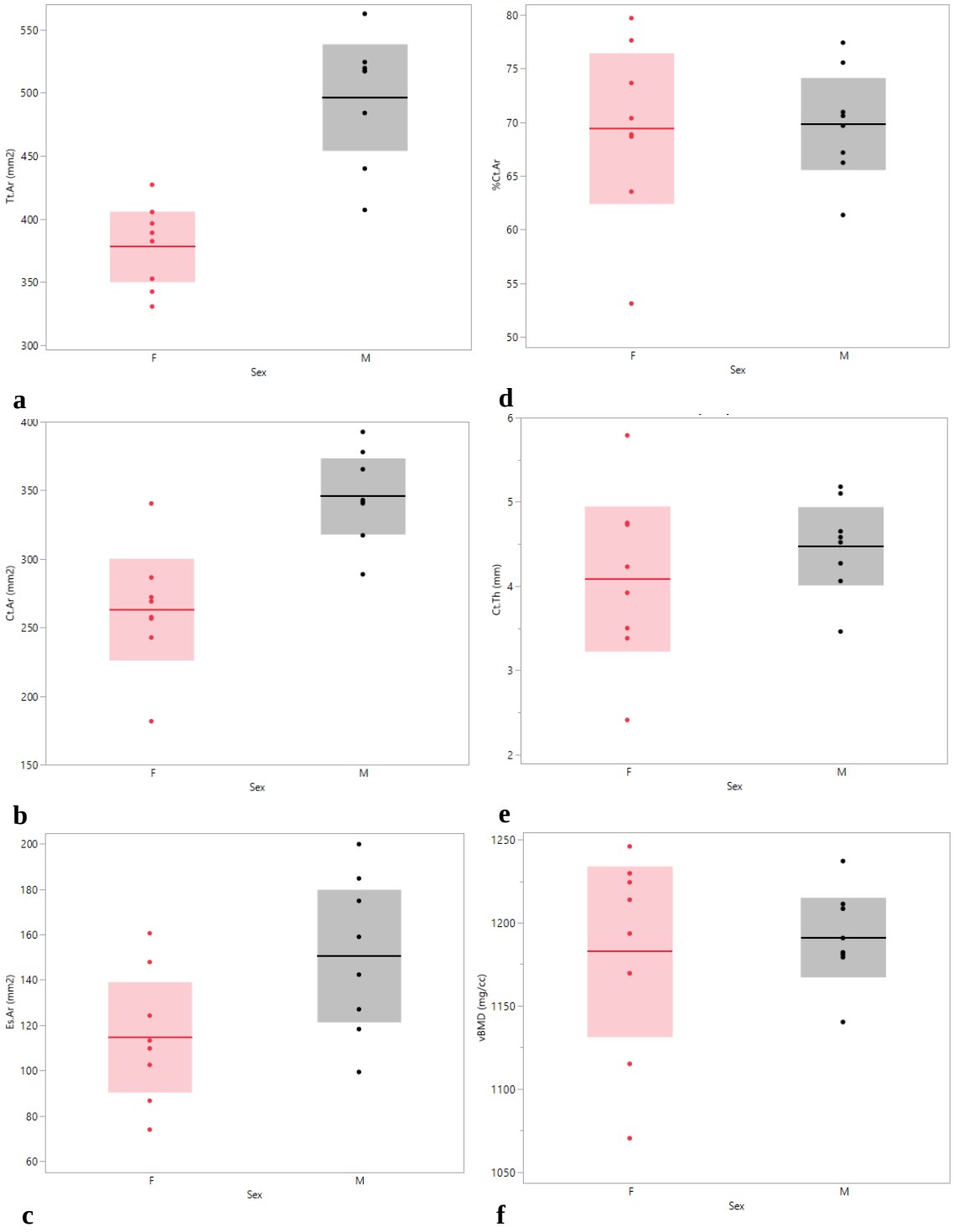

Figure 5. Sex differences boxplots. Display of sex differences in the mean and standard deviation of (a) Tt.Ar (b) Ct.Ar (c) Es.Ar (d) %Ct.Ar (e) Ct.Th and (f) vBMD.

Table 9. T-Test results assessing sex differences in continuous predictor variables.

Variable	DF	t statistic	Estimated M-F Difference	Estimated M-F Difference	Estimated M-F Difference	p-value	Power
				Lower 95%	Upper 95%		
Age	13.99	0.01	0.13	-25.34	25.59	0.99	5.00%
Tt.Ar	12.13	5.52	118.41	71.74	165.07	**<0.01***	99.92%
Ct.Ar	12.98	4.22	82.56	40.24	124.89	**<0.01***	97.45%
Es.Ar	13.55	2.23	35.84	1.25	70.43	**0.04***	54.59%
%Ct.Ar	11.58	0.12	0.43	-7.19	8.05	0.90	5.15%
Ct.Th	10.76	0.94	0.39	-0.53	1.30	0.37	14.11%
vBMD	9.9	0.35	8.50	-44.97	61.96	0.73	6.26%

* Value is significant at $\alpha = 0.05$

Age-Associated Changes in Tibia-Level Variables

Significant relationships between age and Es.Ar (p=0.02) and age and %Ct.Ar (p=0.03) were observed in this study (Table 10). In the pooled sample, with age, Es.Ar increased and %Ct.Ar decreased. These findings are supported by previous research, as endosteal resorption and cortical bone loss are age-related changes exhibited in the tibia diaphysis experienced by both males and females[11]. Although not all tibia-level variables displayed significant relationships with age, the general trends did not differ from what was expected. As age increased, Ct.Ar, %Ct.Ar, Ct.Th, and vBMD decreased (Figure 6). Additionally, as age increased, Es.Ar and Tt.Ar increased (Figure 6). These trends match what was expected, as periosteal expansion in males, endosteal expansion in both sexes, bone loss in both sexes, and decreasing bone mineral density in both sexes are previously documented age-related changes[11,18,19]. Bone loss is an indicator of decreased bone health and increased fracture risk, meaning age-related changes in tibia-level variables are

important relationships to consider when assessing both fracture risk and fracture severity.

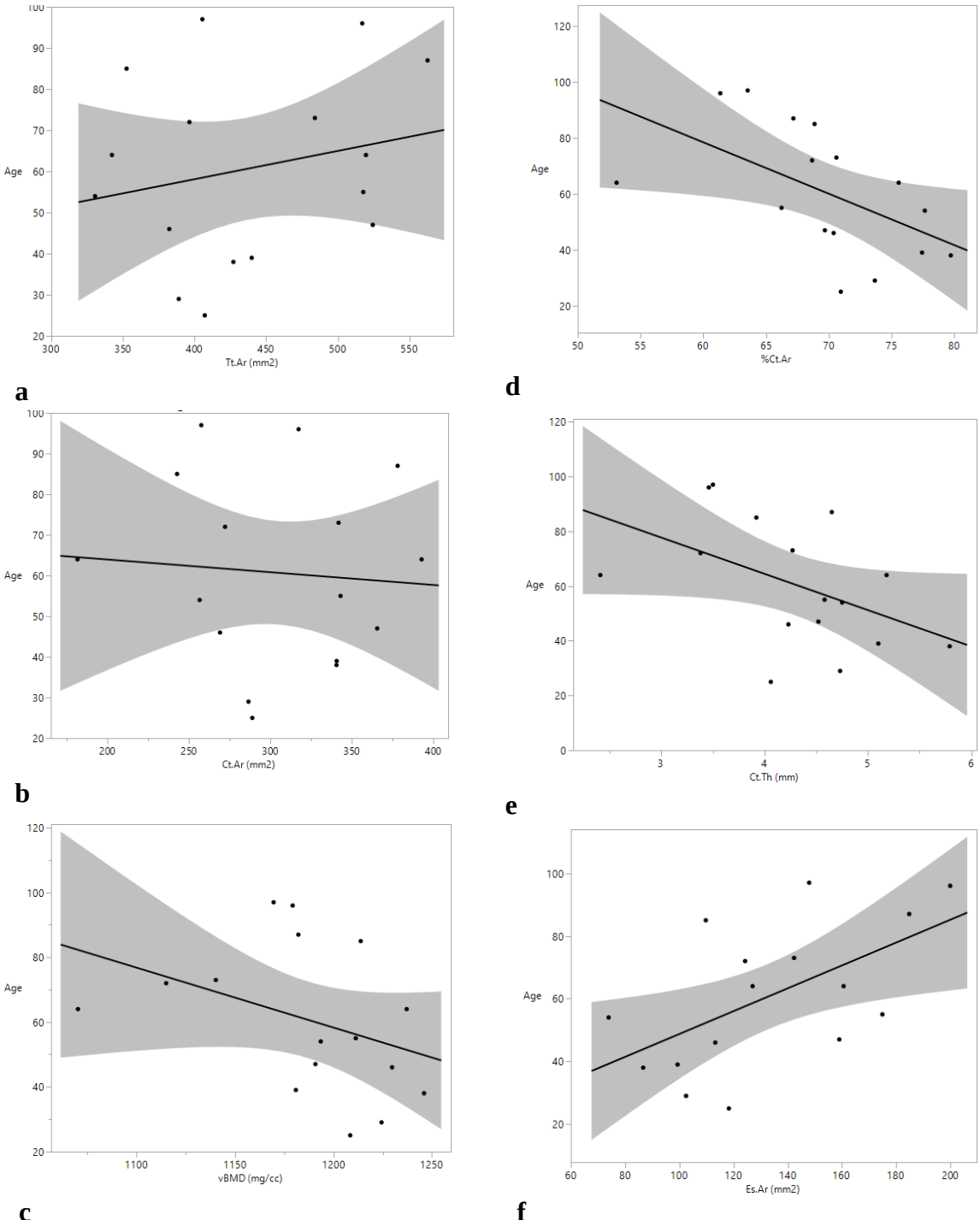

Figure 6. Linear regression and confidence intervals. Display of age (years) as predicted by (a) Tt.Ar (b) Ct.Ar (c) Es.Ar (d) %Ct.Ar (e) Ct.Th and (f) vBMD.

Table 10. Linear regression analysis. Assessment of normality and relationships between age and tibia-level variables.

Term	Estimate	Std Error	t Ratio	p-value	Power
(Intercept)	30.61	35.87	0.85	0.41	5.00%
Tt.Ar	0.07	0.08	0.85	0.41	5.00%
(Intercept)	70.23	33.19	2.12	0.05	34.82%
Ct.Ar	-0.031	0.11	-0.29	0.77	5.00%
(Intercept)	12.28	19.05	0.64	0.53	5.00%
Es.Ar	0.36	0.14	2.63	**0.02***	54.20%
(Intercept)	188.80	53.65	3.52	<0.01*	82.19%
%Ct.Ar	-1.84	0.77	-2.40	**0.03***	45.48%
(Intercept)	117.44	28.41	4.13	<0.01*	92.93%
Ct.Th	-13.25	6.52	-2.03	0.06	31.76%
(Intercept)	280.51	145.13	1.93	0.07	28.24%
vBMD	-0.19	0.12	-1.52	0.15	15.08%
Term	**RMSE**	**R^2**	**R^2 adj.**	**Shapiro-Wilk W**	**Shapiro-Wilk p-value**
Tt.Ar	23.16	4.90%	-1.89%	0.96	0.58
Ct.Ar	23.67	0.61%	-6.49%	0.96	0.66
Es.Ar	19.43	33.04%	28.26%	0.96	0.63
%Ct.Ar	19.99	29.12%	24.06%	0.93	0.20
Ct.Th	20.87	22.77%	17.26%	0.97	0.82
vBMD	22.01	14.10%	7.96%	0.93	0.25

* Value is significant at $\alpha = 0.05$; significant Intercepts do not affect results

Tibia-Level Variables as Predictors of Fracture Number

No significant relationships were found between the tibia-level predictor variables and fracture number group (Table 11). However, trends between tibia-level variables and fracture number group were observed (Figure 9). Individuals that exhibited two or more fractures demonstrated relatively higher Ct.Ar, %Ct.Ar, Ct.Th, and vBMD than individuals that exhibited one fracture (Figure 9). As males make up the majority of individuals exhibiting two or more fractures, the greater Ct.Ar, %Ct.Ar, and Ct.Th values associated with sex-dependent size differences in the tibia were expected[18,19].

Correlations between tibia-level variables were analyzed to determine how tibia-level variables interact with one another (Figure 7). Es.Ar is significantly negatively correlated with %Ct.Ar (r = -0.75), Ct.Th (-0.46), and vBMD (r = -0.36), as endosteal resorption decreases the fraction of cortical bone and bone mineral density. Conversely, Es.Ar is positively correlated with Tt.Ar (r = 0.66) and Ct.Ar (r = 0.22), as periosteal apposition and endosteal resorption are age-related changes that occur in tandem[11]. Interpretation of how tibia-level variables interact is important in assessing changes in bone morphometry associated with age and sex, which can then be used to identify populations at risk for heightened fracture severity when these interactions are compared to fracture number group data.

Principal components analysis was conducted in order to analyze the continuous variables included in this study (individual- and tibial-level variables) grouped by fracture number group (Figure 9). The most important dimension, accounting for 51.5% of variance between fracture number groups, is described by variables contributing to bone size (Tt.Ar, Ct.Ar, Es.Ar) (Figure 9). The second most important dimension, accounting for 34.1% of variance between fracture number groups, includes variables that describe the fraction of cortical bone within the Tt.Ar (Ct.Th, %Ct.Ar, vBMD) (Figure 9). From the PCA, it can be concluded that most variance between fracture number groups can be explained by bone morphometric components. Larger, male tibiae exhibited higher fracture numbers than smaller, female tibiae.

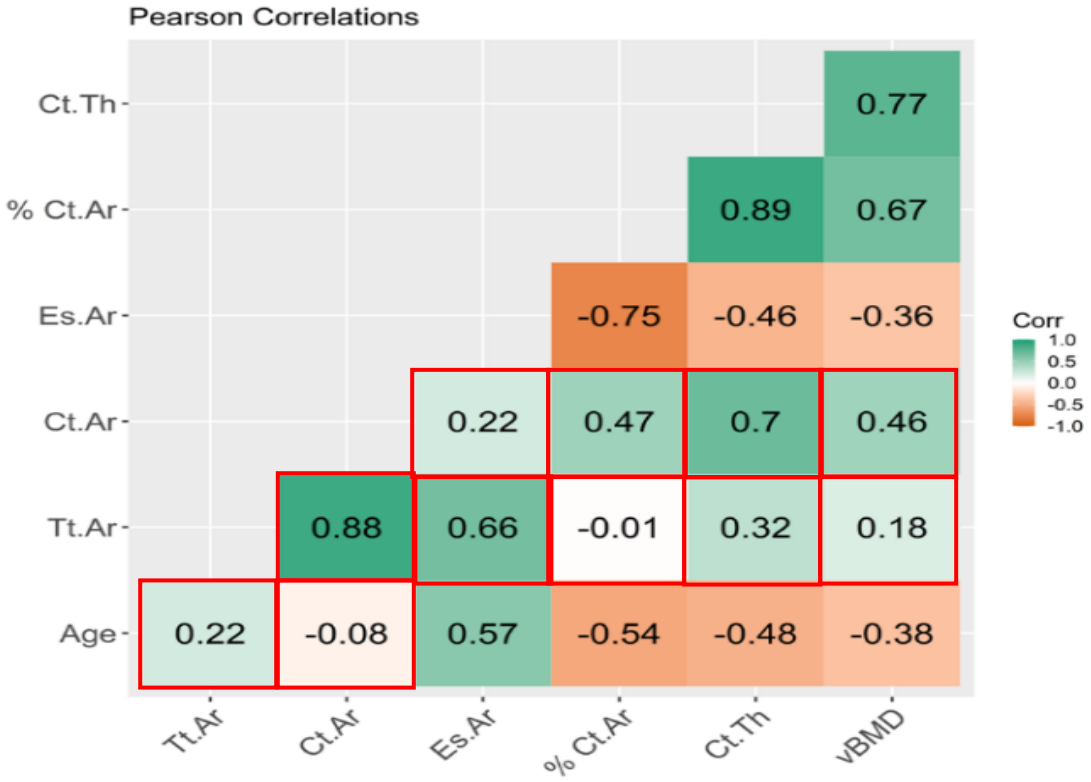

Figure 7. Correlation matrix. Pearson correlation coefficients between continuous variables with significant correlations outlined in red.

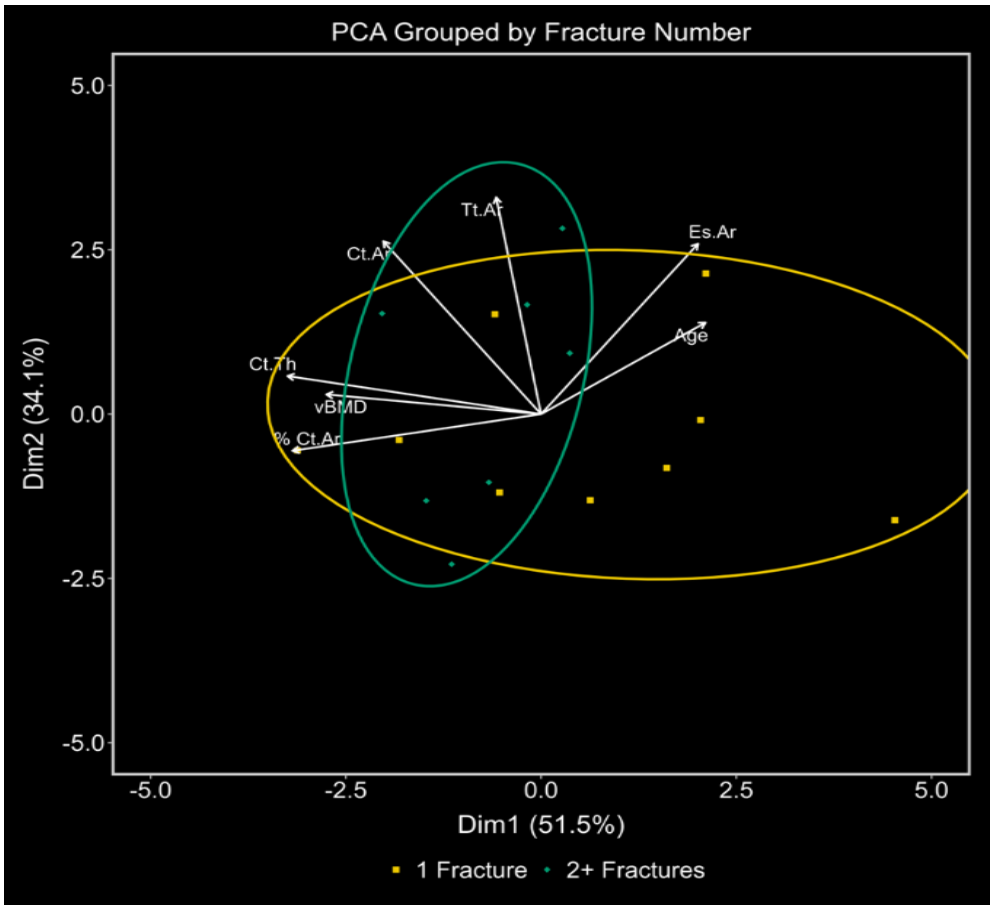

Figure 8. Principal components analysis. Analysis of continuous variables (individual- and tibial-level variables) grouped by fracture number group.

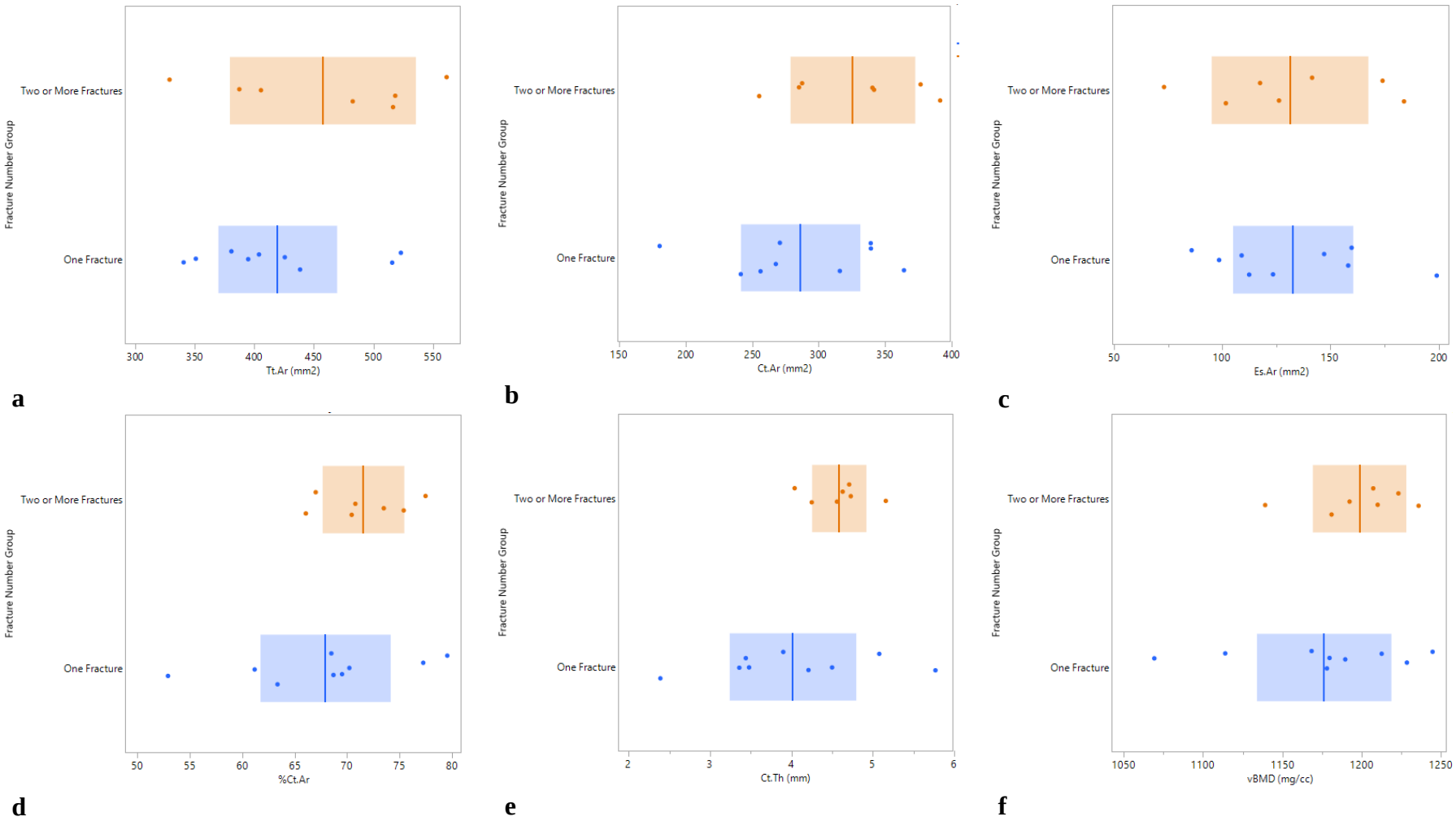

Figure 9. Fracture number group differences boxplots. Differences between fracture number group in the mean and standard deviation of (a) Tt.Ar (b) Ct.Ar (c) Es.Ar (d) %Ct.Ar (e) Ct.Th and (f) vBMD.

Table 11. Ordinal logistic regression. Analysis of relationships between tibia-level variables and fracture number group for the whole sample.

Variable	Estimate	Std Error	Chi-Square	p-value	R^2	Lack of Fit Chi-Square	Lack of Fit p-value
(Intercept)	-3.62	3.33	1.18	0.28			
Tt.Ar	0.01	0.01	1.06	0.30	5.11%	20.81	0.12
(Intercept)	-4.76	3.43	1.92	0.17			
Ct.Ar	0.02	0.01	1.81	0.18	9.71%	19.80	0.14
(Intercept)	-0.09	1.98	0.00	0.96			
Es.Ar	<-0.01	0.01	0.01	0.93	0.03%	21.92	0.08
(Intercept)	-6.97	6.44	1.17	0.28			
%Ct.Ar	0.10	0.09	1.11	0.29	5.88%	20.64	0.11
(Intercept)	-4.79	3.53	1.85	0.17			
Ct.Th	1.05	0.80	1.74	0.19	9.86%	19.77	0.14
(Intercept)	-15.01	15.66	0.92	0.34			
vBMD	0.01	0.01	0.89	0.34	4.71%	20.90	0.10

Overall, individual-level variables and tibia-level variables did not significantly predict fracture number group. Although no significant relationships were found, general trends were observed in this study. Most of the variance between sexes and between fracture number group can be explained by morphological features of the tibia (Ct.Ar, Es.Ar, Tt.Ar). In this study, males had significantly larger tibia dimensions [Tt.Ar ($p<0.01$), Ct.Ar ($p<0.01$), Es.Ar ($p=0.04$)] than females. Additionally, in this study most males (n=5) exhibited 2+ fractures, while most females (n=6) exhibited one fracture.

This study suggests that lower fracture numbers in females could be attributed to the smaller cortical bone area found in females in comparison to males. A preliminary investigation completed by Cole et al. focusing on relationships between cortical porosity and fracture type in human tibiae found that greater % porosity, or the amount of cortical

area attributed to pore spaces, and the convergence of pores into large pore systems, an age-related change in cortical bone, may facilitate more of a direct fracture propagation through the cortex[21]. Increased porosity in females with age, in tandem with the slender nature of female tibiae in comparison to male tibiae, may allow traumatic forces to travel through the cortex without propagation into multiple fractures. In order to more thoroughly understand the relationship between individual-level variables, tibia-level variables, and fracture severity, future research should include a larger sample size, expanded tibia-level variables, and the types of fractures being analyzed to make conclusions regarding complexity, and severity, of fractures.

Limitations

First, since this study utilized PMHS, it is a cross-sectional study. Age-related changes could not be measured longitudinally, so conclusions about age-related trends in this study are made based on the sample age distribution as a whole. The sample size included in this study [n=16 (8 males, 8 females)] likely contributed to the lack of significant results between individual-level variables and fracture number group and tibia-level variables and fracture number group. Future research endeavors will include a larger sample size, allowing for relationships to be more clearly identified. Additionally, future research will include specifications on the type of fracture in addition to the number of fractures, as the number of fractures alone may be facilitating conclusions misrepresenting severity and complexity of fractures. In addition to widening the scope of the fracture characteristic variables, additional tibia-level variables will be included in

future research to build on Cole et al.'s assessment of potential histomorphometric contributions to fracture severity[21].

Conclusion

In this study, significant sex differences were observed in tibia-level variables including Tt.Ar ($p<0.01$), Ct.Ar ($p<0.01$), and Es.Ar ($p=0.04$), which aligns with previous research suggesting that males have larger bones overall than females[17,18].

Additionally, significant relationships between age and tibia-level variables, specifically Es.Ar ($p=0.02$) and %Ct.Ar ($p=0.03$), were observed in this study. With age, Es.Ar increased and %Ct.Ar decreased, which was supported by previous studies examining age-related changes in cortical bone[11]. Other age-related trends, including decreased Ct.Ar, Ct.Th, and vBMD and increased Tt.Ar with age were observed. These trends were supported by previous research identifying age-related changes in bone[11,18,19].

No significant relationships were established between individual-level variables and fracture number group or between tibia-level variables and fracture number group. However, trends between individual-level variables and fracture number group and tibia-level variables and fracture number group were observed. This study found that single fractures were more common in females, and males more often exhibited two or more fractures. Additionally, this study did not identify age-related differences in fracture number group. These results contrast the results found by Harden et al., which did not identify significant relationships between sex and fracture number but identified significant relationships between age and fracture number[12].

Principal components analysis grouping continuous variables by sex and by fracture number group identified that the majority of variance between sexes and between fracture number group (51.5%) is described by variables contributing to bone size (Tt.Ar, Ct.Ar, Es.Ar).

This study suggests that lower fracture numbers in females could be attributed to the smaller tibia size of females in comparison to males. This study demonstrates that traumatic force applied to the tibia leads to more fractures, and thus a more severe injury, in males. Larger bones, and thus larger areas of cortical bone, may facilitate increased fracture numbers in males as larger bones allow for propagation of multiple fractures.

To more thoroughly understand the relationship between individual-level variables, tibia-level variables, and fracture numbers, a larger sample size should be included. Additionally, a wider range of tibia-level variables including histomorphometric and material aspects of bone should be included in future studies in order to further investigate populations susceptible to higher tibia fracture severity, as increased tibia severity is associated with financial, social, and physical burdens negatively affecting quality of life.

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