DR. TROY LABOUNTY (Orcid ID : 0000-0002-9674-5212)

PROF. EDUARDO BOSSONE (Orcid ID : 0000-0003-2769-9950)

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Indexing Left Ventricular Wall Thickness to Body Surface Area Improves Prognostic Value

Troy M. LaBounty, MD[a]; David S. Bach, MD[a]; Eduardo Bossone, MD[b]; Theodore J. Kolias, MD[a]

[a]Department of Medicine, University of Michigan, 1500 E Medical Center Dr., Ann Arbor, MI 48109. Email: labt@med.umich.edu

[b]Heart Department, University Hospital, Salerno, Italy. Email: ebossone@hotmail.com

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Corresponding Author: Troy LaBounty, MD; University of Michigan Medical Center, 1500 E Medical Center Dr., SPC 5853, Room 2365, Ann Arbor MI 48109-5853. Email: labt@med.umich.edu; phone: 734-764-7440; fax: 734-232-4132.

ABSTRACT

BACKGROUND: Guidelines provide normal ranges of left ventricular (LV) wall thicknesses (WT) without indexing. We hypothesized that indexing WT to body surface area (BSA) improves prognostic value.

METHODS: We examined the relationship between WT and BSA in 9,737 patients undergoing echocardiography without risk factors for LV hypertrophy other than obesity. We compared WT to BSA and examined the relationship of WT and LV mass index (LVMI) to mortality.

RESULTS: There is a linear relationship between BSA and septal and posterior WT ($r=0.38$, $p<0.001$ for each). Higher quartiles of BSA were associated with increased WT ($p<0.001$). After adjusting for age and gender, greater mean WT (MWT) (Hazards Ratio [HR] 1.10 per mm, 95% Confidence Interval [CI] 1.04 to 1.16, $p=0.001$, c-statistic 0.66), LVMI (HR 1.01, 95% CI 1.001-1.01, $p=0.01$, c-statistic 0.66), and indexed MWT (HR 1.34 per mm/m^2, 95% CI 1.23 to 1.47, $p<0.001$, c-statistic 0.67) are each associated with increased mortality, with indexed MWT having the highest prognostic value. Each decile of indexed MWT ≥8th decile was associated with increased mortality compared to the 1st decile ($p<0.01$ for each). Individuals with indexed MWT ≥8th decile (≥5.0 mm/m^2) had increased adjusted mortality (HR 1.67, 95% CI 1.43-1.94, $p<0.001$, c-statistic 0.67); this had improved prognostic value over guideline definitions of increased MWT (c-statistic 0.66) or LVMI ($p=$NS).

CONCLUSIONS: We observe a linear relationship between BSA and WT. Indexing WT improves mortality prediction over LVMI and non-indexed WT. These findings support indexing WT to BSA.

KEY WORDS: left ventricular hypertrophy; echocardiography; outcomes

Most cardiac structures have been demonstrated to have a relatively linear relationship to body size, and are commonly indexed to body surface area (BSA) to define abnormal values.[1] Left ventricular (LV) wall thickness (WT) on magnetic resonance imaging has a linear relationship to BSA as noted in the Multi-Ethnic Study of Atherosclerosis,[2] but current echocardiographic guidelines recommend that increased WT should be defined as ≥10 mm in women and ≥11 mm in men without indexing for body size.[1] Identification

of LV hypertrophy on echocardiography carries significant prognostic implications.[1, 3] While LV mass index (LVMI) is more accurate than increased non-indexed WT for identification of LV hypertrophy,[4] it also requires complex calculation, and previous guidelines have recognized that measurement of WT may be the easiest approach to identify these patients in clinical practice.[5] Our hypothesis was that LV WT on echocardiography has a linear relationship to body size, and we compared the relationship between WT and both BSA and height. Further, we hypothesized that indexed mean WT (I-MWT) would have improved prognostic value over non-indexed mean WT (MWT). We therefore examined the relationship between WT and body size in a population without known cardiovascular disease undergoing echocardiography, and compared the prognostic significance of MWT, LVMI, and I-MWT.

METHODS

We examined WT in adult patients referred for a clinically indicated transthoracic echocardiogram. As recommended by recent guidelines for assessment of reference values with 2-dimensional echocardiography,[1] we examined a population without known cardiovascular disease and without known risk factors for increased WT by excluding individuals with a systolic blood pressure >140 mmHg or diastolic blood pressure >80 mmHg (mean of 3 values), estimated glomerular filtration rate <60 ml/min/1.73m^2, or history of hypertension, diabetes, or hyperlipidemia. We did not exclude obese individuals as we specifically wanted to evaluate the relationship between LV WT and body size. We further excluded individuals with hypertrophic cardiomyopathy (clinical diagnosis or any WT≥15 mm as per guidelines),[6] myocardial infarction, or prior valve replacement. Finally, we excluded individuals with echocardiographic findings of aortic stenosis, aortic regurgitation, at least moderate mitral regurgitation, or a LV ejection fraction <50% (echocardiographic exclusion criteria). From a total population of 60,504 individuals with a complete echocardiogram during 2012 through 2015, 11,483 individuals remained after applying clinical exclusion criteria. An additional 1,370 subjects were excluded after applying echocardiographic exclusion criteria. Finally, we excluded patients with inadequate image quality for measurements of LV diameter and WT (n=495); and patients without recorded BSA (n=42). This resulted in a final cohort of

9,737 individuals in the study. In patients with multiple studies, we used the first available study. The study was approved by the Institutional Review Board with a waiver of informed consent. The study is consistent with the Declaration of Helsinki.

Echocardiograms were performed at a tertiary care academic medical center, 1 of 6 affiliated satellite clinics located in 5 cities, and an affiliated private practice primary care hospital in a 6th city; sites were located within 3 adjacent counties. All studies were performed by experienced registered cardiac sonographers and interpreted by a core group of cardiologists with Level III training in echocardiography within a single lab. Echocardiography performance followed recommended standardized guidelines and included comprehensive study of all cardiac structures.[7] Echocardiograms were performed using Philips EPIQ 7 and iE33 systems (Philips Healthcare, Andover, MA); Acuson Sequoia 512 systems (Siemens, Malvern, PA); or GE Vivid 7, Vivid 9, or Vivid E9 systems (GE Healthcare, Wauwatosa, WI). Images were archived in standard DICOM format, and reviewed using contemporary versions of Synapse Cardiovascular Client (Fujifilm Medical Systems, Valhalla, NY). Echocardiography measurements were performed in accordance with guidelines, with WT and LV diameters performed using parasternal long-axis views from 2D echocardiography.[1] LV mass was calculated using the Cube formula as recommended in guidelines.[1]

Clinical data were extracted from the electronic medical record. All-cause mortality was assessed within the electronic medical record based on its query of state and federal death records. Body surface area was calculated using the Du Bois, Du Bois formula. Obesity was defined as body mass index ≥30 kg/m^2.

Data were tested for normal distribution using the Kolmogorov-Smirnov test. Continuous variables were compared using t-tests and ANOVA for variables with normal distributions and the Mann-Whitney U test and Kruskal-Wallis test for variables without a normal distribution. Pearson correlations were used to compare the linear relationship between continuous variables. To simplify comparisons for outcome analyses, the mean values of WT (mean of septal and posterior walls) were used for all analyses unless specified. Kaplan-Meier curves with the log-rank test and Cox regression analyses adjusted for age and gender were used to compare the relationship between WT and mortality using thresholds defined by guidelines and a threshold

defined as elevated risk by decile of I-MWT. C-statistics were calculated from logistic regression models including age and gender. P-values <0.05 were considered significant. Statistical analyses were performed using IBM SPSS version 24 for Mac (IBM Corporation; Armonk, NY).

RESULTS

Mean age was 49.9 ±15.7 years, and 61.4% (5982/9737) were female. Mean BSA was 1.90 ±0.26 m^2, and mean height was 1.69 ±0.10 m. Mean body mass index was 28.0±6.8 kg/m^2; 30.1% of individuals were obese. There were 689 deaths, and mean follow-up was 2.4±1.1 years.

There is a linear relationship (Figures 1A and 1B) between septal WT and BSA (r=0.39 overall, r=0.29 for women, r=0.29 for men, p<0.001 for each), and between posterior WT and BSA (r=0.38 overall, r=0.29 for women, r=0.29 for men, p<0.001 for each). A statistically significant but weaker linear relationship was observed (Figure 1C) between septal WT and height in the overall cohort (r=0.24, p<0.001) and in men (r=0.10 for men, p<0.001), but not in women (r=0.02, p=0.08). Similarly, there was a linear relationship (Figure 1D) between posterior WT and height in the overall group (r=0.25 overall, p<0.001), in women (r=0.05, p<0.001), and in men (r=0.12, p<0.001).

Tables I and II provide median LV septal and posterior WT by quartile of BSA and height in the overall cohort as well as by gender, and demonstrate a significant increase in WT with higher quartiles of BSA and height. Given the higher linear relationship between WT and BSA as compared to height, as well as its consistency across genders, further analyses were limited to indexing WT to BSA.

Using current guideline definitions of increased non-indexed WT (≥10 mm for women and ≥11 mm for men)[1] in this population without known risk factors other than obesity, increased WT was observed with greater frequency in subjects with higher BSA quartiles (Figure 2).

Using the mean of the septal and posterior walls, the median indexed wall thickness was 4.6 mm/m^2 (interquartile range 4.1-5.1). There was a small difference in median indexed WT between females (4.6 mm/m^2, interquartile range 4.2-5.2) and males (4.5 mm/m^2, interquartile range 4.1-5.0; p<0.001).

Increased septal WT (HR 1.09 per mm, 95% CI 1.04-1.14, p<0.001), posterior WT (HR 1.08 per mm, 95% CI 1.03-1.13, p=0.003), septal WT/BSA (HR 1.30 per mm/m^2, 95% CI 1.20-1.41, p<0.001), and posterior WT/BSA (HR 1.29 per mm/m^2, 95% CI 1.19-1.41, p<0.001) are each associated with increased mortality.

Both before and after adjusting for age and gender, greater MWT, LVMI, and I-MWT are each associated with increased mortality, with the highest C-statistic observed with I-MWT (Table III).

To identify a possible threshold for risk based on I-MWT, we examined mortality stratified by decile of I-MWT. Figure 3 demonstrates significant differences between groups (log rank p<0.001). After adjusting for age and gender, and using the 1^{st} decile as a reference, only the 8^{th} (HR 1.12, 95% CI 1.06-1.18, p<0.001), 9^{th} (HR 1.08, 95% CI 1.03-1.13, p=0.003), and 10^{th} (HR 1.09, 95% CI 1.05-1.14, p<0.001) decile groups had increased mortality; all other deciles had no difference in adjusted mortality compared to the 1^{st} decile (p>0.05 for each). The $\geq 8^{th}$ deciles of I-MWT correspond to a measurement of ≥ 5.0 mm/m^2.

Table IV demonstrates the prognostic value of MWT and LVMI using current guideline recommendations to define elevated values,[1] with the addition of I-MWT ≥5.0 mm/m^2 ($\geq 8^{th}$ decile with highest observed risk). Of these, I-MWT has the highest prognostic value based on the C-statistic.

DISCUSSION

In a population without known risk factors for LV hypertrophy, we observed a linear relationship between body size and WT, with the strongest relationship seen using BSA. We observed a stronger linear relationship between WT and BSA in comparison to height, and this relationship remained significant for both septal and posterior walls among both genders, unlike height. These results are consistent with findings using cardiac magnetic resonance imaging in the Multi-Ethnic Study of Atherosclerosis study, which observed a linear relationship between WT and BSA, but not height.[2]

Using current guideline definitions, elevated non-indexed WT was common in our population without known risk factors for LV hypertrophy, and became increasingly

frequent among larger patients; this may in part be due to the high prevalence of obesity. Nearly half of inviduals (including the majority of women) in the top quartile of BSA would be classified as having increased WT, which could result in reporting LV hypertrophy. Calculation of LVMI could allow indexing to BSA, but this is not always readily available in clinical practice, as recognized by prior guidelines.[5]

An important role for imaging tests is to identify patients at increased risk of adverse events. We observed that I-MWT as a continuous variable had improved prognostic performance over either MWT or LVMI in our population, with a higher C-statistic. It is surprising that LVMI did not have superior prognostic performance, although the Cube formula used to calculate it is based on geometric assumptions and has a potential for error.[1] While I-MWT appeared superior to LVMI for prognostic assessment in our population, there is extensive evidence supporting the prognostic value of LVMI,[1, 3, 8-10] and further research may be warranted.

Unlike the continuous relationship that has been previously observed between LVMI and risk of adverse events in hypertensive patients,[11] we observed a different pattern in this cohort. In our study, individuals in the 1st through 7th deciles of I-MWT had no statistically significant difference in adjusted mortality using the 1st decile as a baseline, although increased mortality was observed in the 8th and higher deciles. When we compared patients above versus below this threshold, the resulting multivariable model demonstrated higher prognostic performance than the models using guideline definitions of LV hypertrophy based on non-indexed WT and LVMI.

Current guideline definitions of increased WT and LVMI are based on a threshold of 1.96 SD above the mean in a normal population. Our normotensive population did not have known risk factors for LV hypertrophy other than obesity[12-16]; however, given the potential for unmeasured variables and given the inclusion of obese individuals in our study, we instead examined the relationship between I-MWT by decile and mortality. Using this, we identified an outcome-based threshold of I-MWT ≥80th percentile, whereas 30% of individuals in our cohort would be defined as having increased mortality, and used this threshold to define an elevated I-MWT in our population. The use of this threshold to define LV hypertrophy had improved prognostic performance over increased non-indexed WT defined by current guidelines, while there was no

statistically significant association in our population between guideline-defined increased LVMI and mortality.

A limitation of this study is that it examined subjects within a limited geographic area, although it does represent echocardiograms performed at 8 sites in 6 cities. In addition, while we excluded individuals with known risk factors other than obesity for LV hypertrophy or increased WT, unmeasured variables may be present. We had a high rate of obese individuals, and our findings may not apply to other populations. Further, we examined individuals referred for clinically indicated echocardiography, which may introduce selection bias. Nevertheless, observations of cutpoints associated with increased risk still may be applicable among populations undergoing clinically indicated echocardiography. While studies of normal volunteers may avoid these biases,[17, 18] these studies would also be susceptible to volunteer bias, and would lack the statistical power of this cohort. In addition, studies were not blindly interpreted, which could also introduce bias. Finally, we did not compare our findings to other allometric models of LV mass or increased wall thickness,[19, 20] but these could be considered in future studies.

We observed a linear relationship between BSA and LV WT in a population without known risk factors for LV hypertrophy other than obesity. In comparison to non-indexed WT or LVMI, I-MWT has improved mortality prediction. These findings support indexing WT to BSA. Further study in other populations are needed to validate these findings and to establish the clinical role of indexing WT to define LV hypertrophy and identify patients at risk.

AUTHOR CONTRIBUTIONS

Troy LaBounty was involved in study design, data analysis, drafting paper, editing, and approval of final manuscript.

David Bach, Theodore Kolias, and Eduardo Bossone were each involved in study design, editing of manuscript, interpretation of findings, and approval of final manuscript.

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TABLES

Table I. Left Ventricular Wall Thickness by BSA

	1st Quartile BSA (<1.71m^2)	2nd Quartile BSA (1.71-1.88m^2)	3rd Quartile BSA (1.89-2.07m^2)	4th Quartile BSA (>2.07m^2)	p
Overall					
Septal WT	8 (7-9)	8 (7-9)	9 (8-10)	10 (9-11)	<0.001
Posterior WT	8 (7-9)	8 (8-9)	9 (8-10)	9 (8-10)	<0.001
Women					
Septal WT	8 (7-9)	8 (7-9)	9 (8-10)	9 (8-10)	<0.001
Posterior WT	8 (7-9)	8 (7-9)	9 (8-9)	9 (8-10)	<0.001
Men					
Septal WT	8 (7-9)	9 (8-10)	9 (8-10)	10 (9-11)	<0.001
Posterior WT	8 (7-9)	8 (8-10)	9 (8-10)	10 (9-11)	<0.001

Median (interquartile range) provided. WT, wall thickness.

Table II. Left Ventricular Wall Thickness by Height

	1st Quartile Height (<1.62m)	2nd Quartile Height (1.63-1.68m)	3rd Quartile Height (1.68-1.77m)	4th Quartile Height (>1.77m)	p

Overall					
Septal WT	8 (7-9)	8 (7-9)	9 (8-10)	9 (8-11)	<0.001
Posterior WT	8 (7-9)	8 (7-9)	9 (8-10)	9 (8-10)	<0.001
Women					
Septal WT	8 (7-9)	8 (7-9)	8 (7-9)	8 (8-10)	0.07
Posterior WT	8 (7-9)	8 (7-9)	8 (7-9)	9 (8-10)	<0.001
Men					
Septal WT	9 (8-10)	9 (8-10)	9 (8-10)	9 (8-11)	<0.001
Posterior WT	9 (8-10)	9 (8-10)	9 (8-10)	9 (8-10)	<0.001

Median (interquartile range) provided. WT, wall thickness.

Table III. Relationship between Continuous Measures of Left Ventricular Hypertrophy and Mortality

	Unadjusted HR (95% CI)	**p**	**Adjusted HR (95% CI)**	**p**	**C-statistic**
MWT (per mm)	1.21 (1.15-1.27)	<0.001	1.10 (1.04-1.16)	<0.001	0.660
LVMI (per gm/m^2)	1.01 (1.01-1.01)	<0.001	1.01 (1.001-1.01)	0.01	0.659
I-MWT (per mm/m^2)	1.50 (1.38-1.62)	<0.001	1.34 (1.23-1.47)	<0.001	0.671

Multivariable models adjust for age and gender. MWT, mean wall thickness; LVMI, left ventricular mass index; I-MWT, indexed mean wall thickness.

Table IV. Relationship between Presence of Left Ventricular Hypertrophy and Mortality using Defined Thresholds

	Unadjusted HR (95% CI)	p	Adjusted HR (95% CI)	p	C-statistic
MWT ≥10 (females) or 11 mm (males)	1.60 (1.38-1.87)	<0.001	1.34 (1.15-1.57)	<0.001	0.662
LVMI ≥96 (females) or 116 gm/m^2 (males)	1.46 (1.11-1.91)	0.007	1.30 (0.99-1.71)	0.06	-
I-MWT ≥5.0 mm/m^2	1.98 (1.71-2.30)	<0.001	1.67 (1.43-1.94)	<0.001	0.673

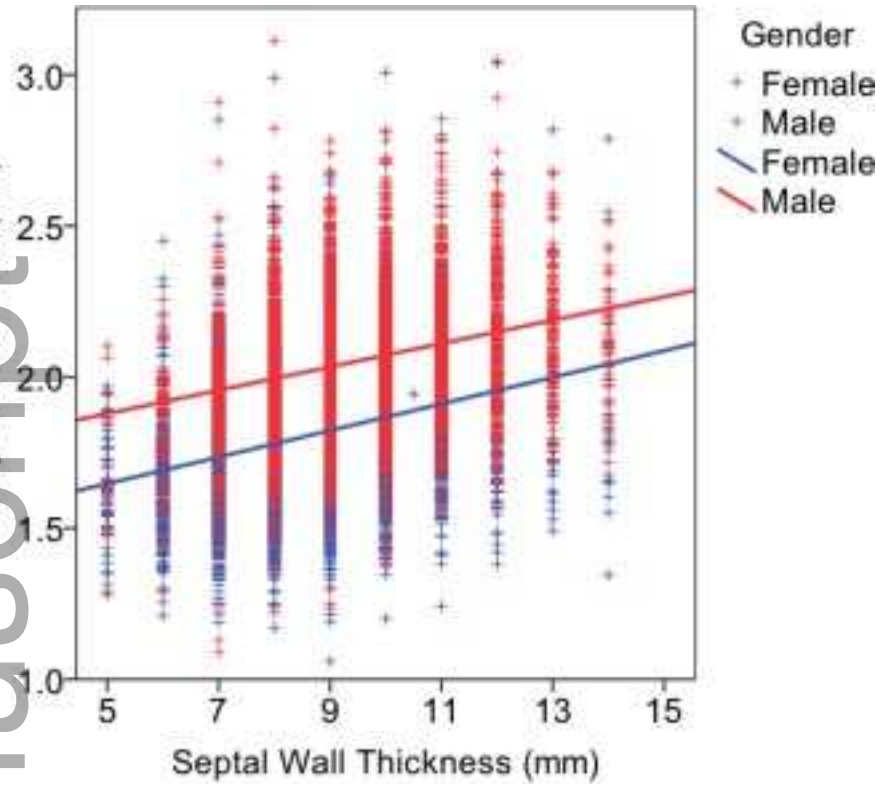
Multivariable models adjust for age and gender. MWT, mean wall thickness; LVMI, left ventricular mass index; I-MWT, indexed mean wall thickness.

FIGURE LEGEND

Figures 1A to 1D. Wall Thickness and Body Size. These figures demonstrate the linear relationship between BSA and septal WT (Figure 1A), BSA and posterior WT (Figure 1B), height and septal WT (Figure 1C), and height and posterior WT (Figure 1D). Color is used to differentiate by gender, and gender-specific reference lines are provided for each. WT, wall thickness.

Figure 2. Percentage of Patients with Increased Wall Thickness Using Current Guidelines by Quartile of BSA. Increased values were defined as either septal or posterior WT ≥10 mm for women and ≥11 mm for men. *p<0.001 versus 1st quartile.

Figure 3. Kaplan-Meier Curve for Mortality by Decile of Indexed Mean Wall Thickness. Log-rank p<0.001.



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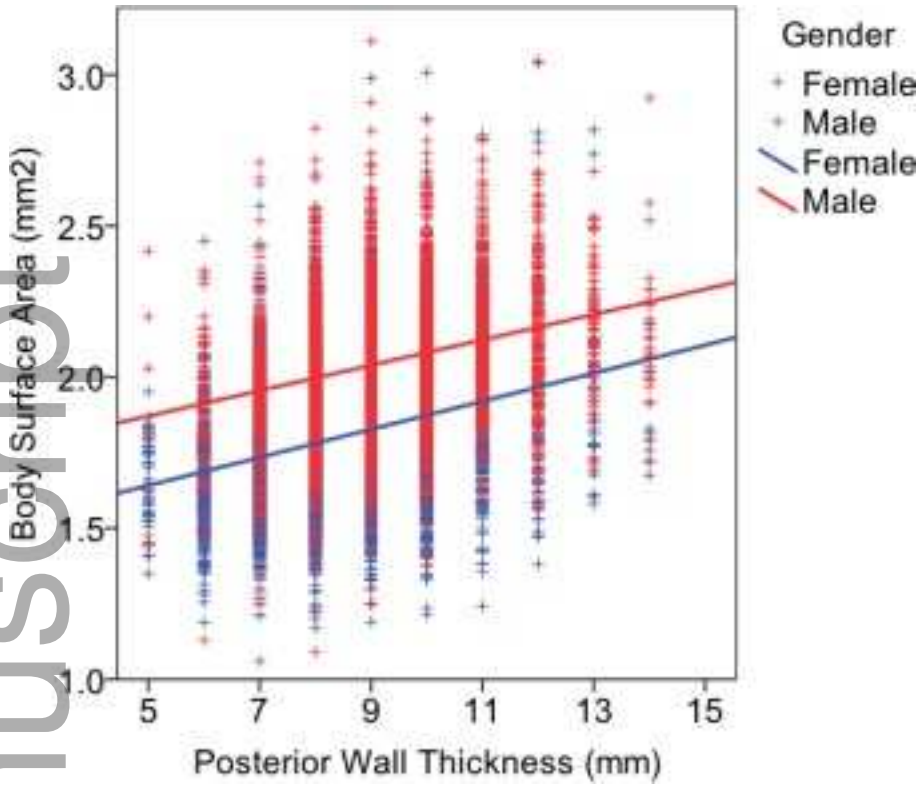

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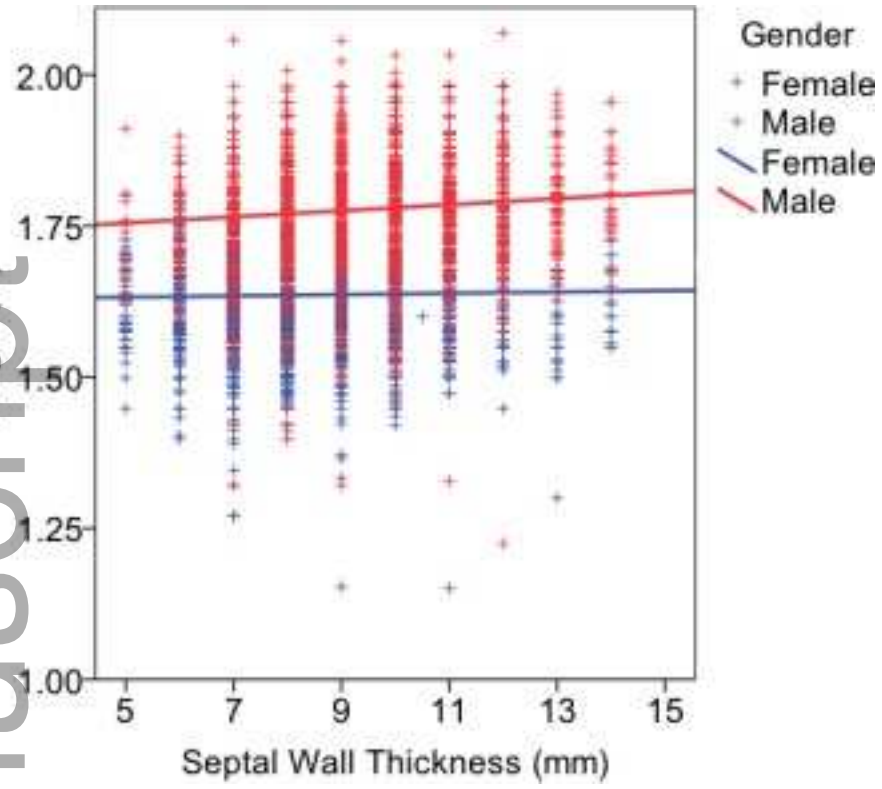

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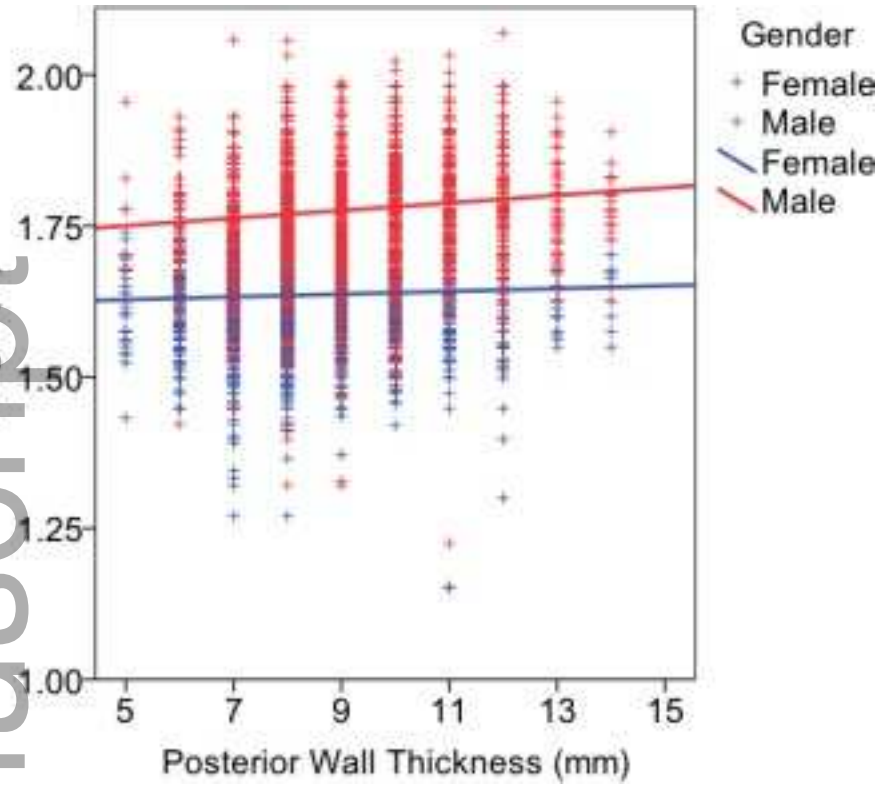

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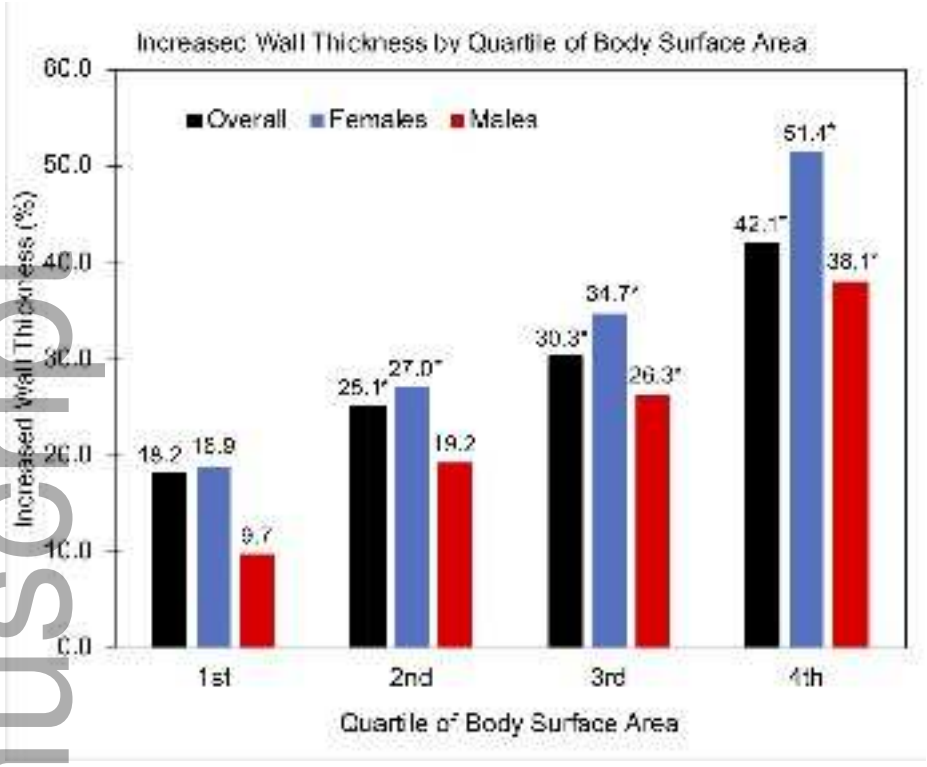

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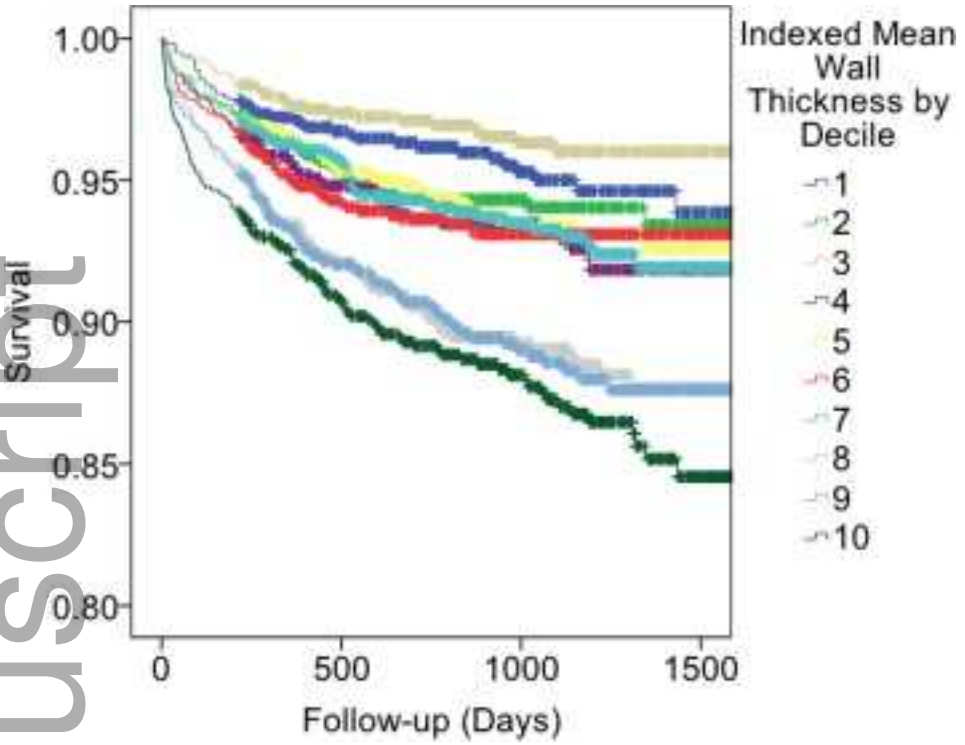

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