ORIGINAL INVESTIGATIONS

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Indexing left ventricular wall thickness to body surface area improves prognostic value

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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 9737 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] 1.04–1.16, $P = 0.001$, 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 1.23–1.47, $P < 0.001$, 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 nonindexed WT. These findings support indexing WT to BSA.

KEYWORDS
echocardiography, left ventricular hypertrophy, outcomes

1 | INTRODUCTION

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 nonindexed 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 nonindexed 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.

2 | 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 mm Hg or diastolic blood pressure >80 mm Hg (mean of three values), estimated glomerular filtration rate <60 mL/min/1.73 m^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 1370 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 9737 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, one of six affiliated satellite clinics located in five cities, and an affiliated private practice primary care hospital in a 6th city; sites were located within three 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).

3 | 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 (Figure 1A,B) 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 1 and 2 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.
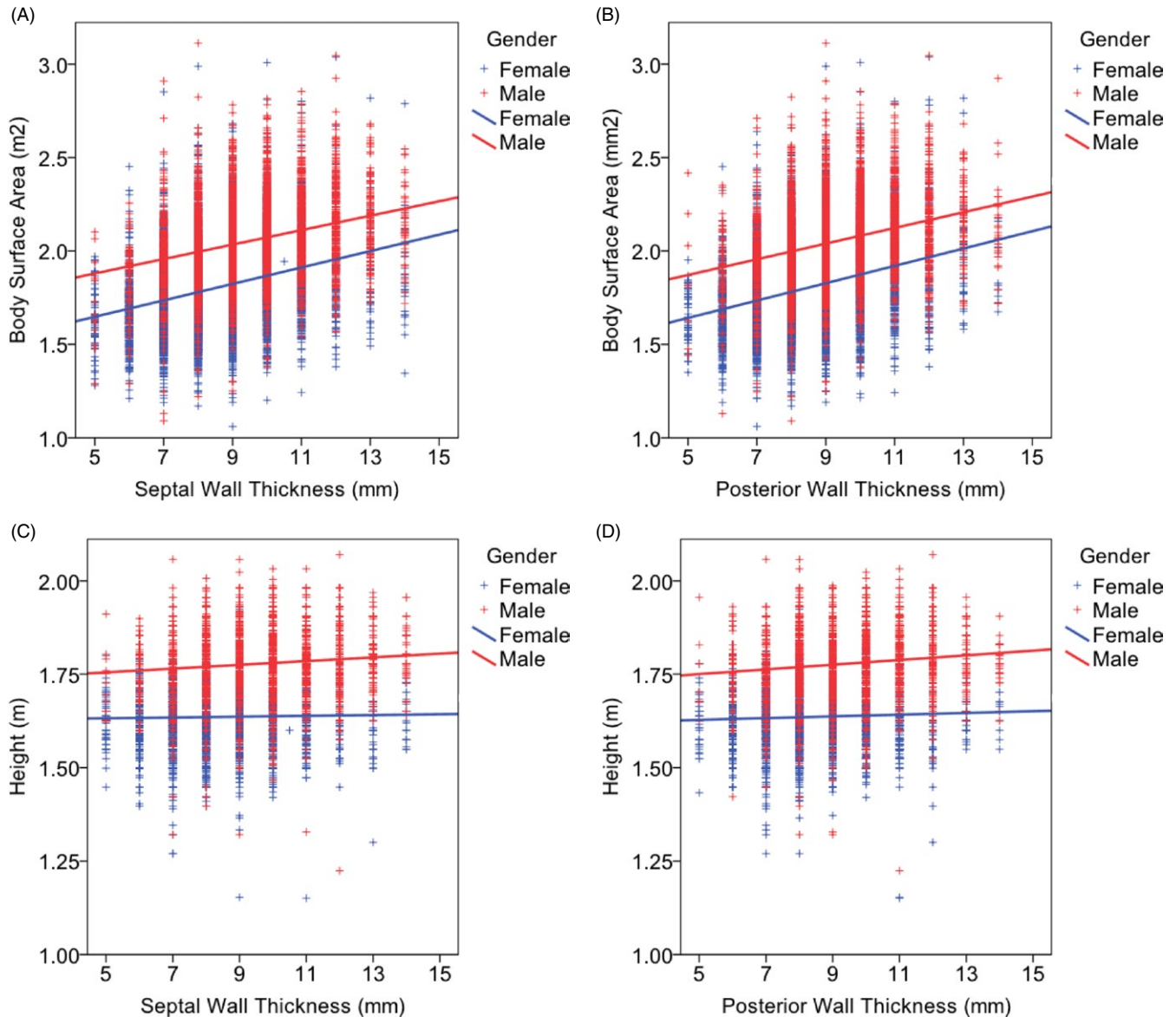
FIGURE 1 A–D, Wall thickness and body size. These figures demonstrate the linear relationship between body surface area (BSA) and septal WT (A), BSA and posterior WT (B), height and septal WT (C), and height and posterior WT (D). Color is used to differentiate by gender, and gender-specific reference lines are provided for each. WT = wall thickness

Using current guideline definitions of increased nonindexed 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 (Hazards Ratio [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 3).

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 1st decile as a reference, only the 8th (HR 1.12, 95% CI 1.06–1.18, $P < 0.001$), 9th (HR 1.08, 95% CI 1.03–1.13, $P = 0.003$), and 10th (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 1st decile ($P > 0.05$ for each). The ≥8th deciles of I-MWT correspond to a measurement of ≥5.0 mm/m^2.

Table 4 demonstrates the prognostic value of MWT and LVMI using current guideline recommendations to define elevated values,[1]

**TABLE 1** Left ventricular wall thickness by body surface area (BSA)

	1st quartile BSA (<1.71 m²)	2nd quartile BSA (1.71–1.88 m²)	3rd quartile BSA (1.89–2.07 m²)	4th quartile BSA (>2.07 m²)	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 2 Left ventricular wall thickness by height

	1st quartile height (<1.62 m)	2nd quartile height (1.63–1.68 m)	3rd quartile height (1.68–1.77 m)	4th quartile height (>1.77 m)	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.
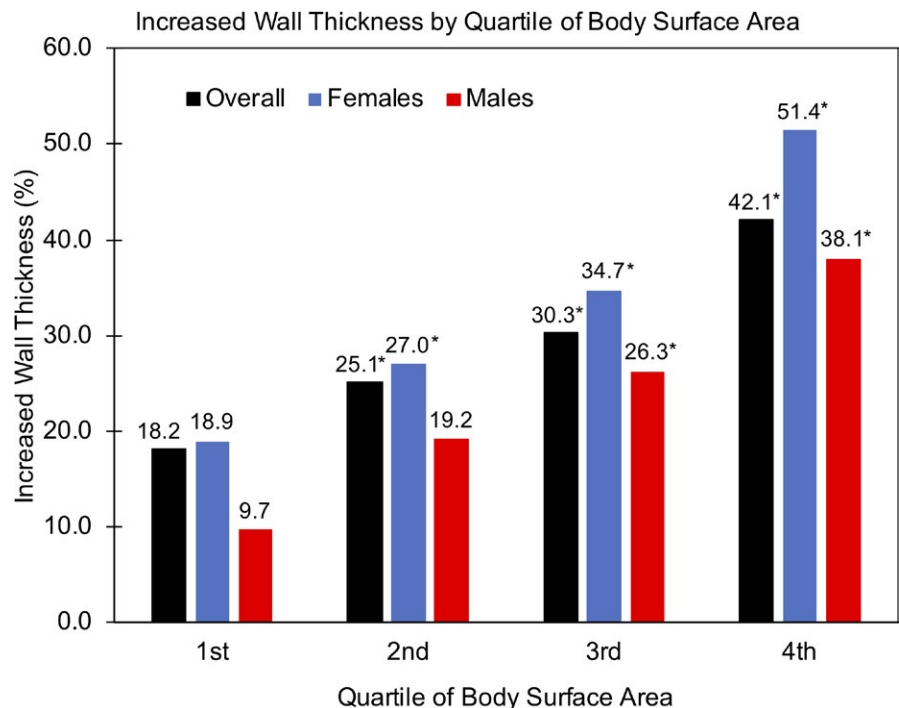
FIGURE 2 Percentage of patients with increased wall thickness using current guidelines by quartile of body surface area. Increased values were defined as either septal or posterior WT ≥10 mm for women and ≥11 mm for men. *P < 0.001 vs 1st quartile

TABLE 3 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 g/m²)	1.01 (1.01–1.01)	<0.001	1.01 (1.001–1.01)	0.01	0.659
I-MWT (per mm/m²)	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. I-MWT = indexed mean wall thickness; LVMI = left ventricular mass index; MWT = mean wall thickness.
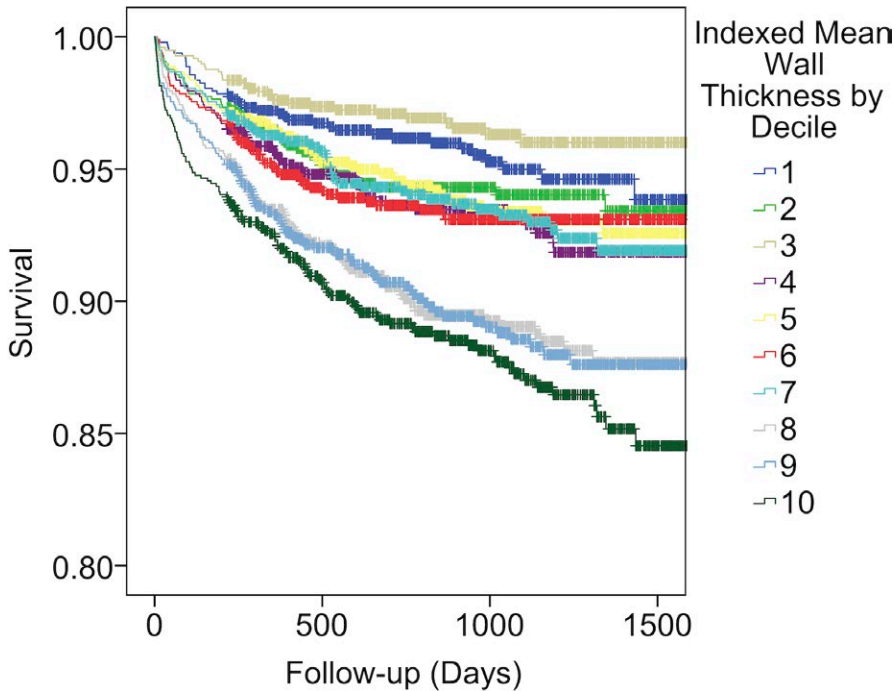
FIGURE 3 Kaplan–Meier curve for mortality by decile of indexed mean wall thickness. Log-rank *P* < 0.001

TABLE 4 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 g/m² (males)	1.46 (1.11–1.91)	0.007	1.30 (0.99–1.71)	0.06	–
I-MWT ≥ 5.0 mm/m²	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. I-MWT = indexed mean wall thickness; LVMI = left ventricular mass index; MWT = mean wall thickness.

with the addition of I-MWT ≥5.0 mm/m² (≥8th decile with highest observed risk). Of these, I-MWT has the highest prognostic value based on the *C*-statistic.

4 │ 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 nonindexed 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 individuals (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 vs below this threshold, the resulting multivariable model demonstrated higher prognostic performance than the models using guideline definitions of LV hypertrophy based on nonindexed 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 nonindexed 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 eight sites in six 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 nonindexed WT or LVMI, I-MWT has improved mortality prediction. These findings support indexing WT to BSA. Further study in other populations is needed to validate these findings and to establish the clinical role of indexing WT to define LV hypertrophy and identify patients at risk.

CONFLICT OF INTEREST

None.

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