

Relationship of Body Fat and Left ventricular hypertrophy with the Risk of All-cause Death in Patients with Coronary Artery Disease

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Original investigation

Keywords: Obesity, Left ventricular hypertrophy, Mortality, Coronary artery disease

Posted Date: March 13th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-296999/v1>

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Abstract

Background and aims

Left ventricular hypertrophy (LVH) is prevalent in obese individuals. Besides, both of LVH and obesity is associated with subclinical LV dysfunction. However, little is known about the interplay between body fat and LVH in relation to all-cause death in patients with coronary artery disease (CAD).

Methods

In this retrospective cohort study, a total of 2243 patients with angiographically proven CAD were included. Body fat and LV mass were calculated using formulas. Higher body fat was defined as the percentage of body fat was greater than 75th percentile. LVH was defined according to guidelines' definition. Patients were divided into four groups: group 1, lower body fat and no LVH; group 2, lower body fat and LVH; group 3, higher body fat and no LVH; group 4, higher body fat and LVH. Cox-proportional hazard models were used to observe the interaction effect of body fat and LVH on all-cause death.

Results

Over 2.2 years, there were 120 deaths. Patients with higher body fat and no LVH (group 3) had similar risk of death (adjusted HR 1.83, 95%CI 1.00-3.38, P = 0.054) compared to the reference group (group 1), while patients with lower body fat and LVH (group 2) had the highest risk (adjusted HR 2.15, 95%CI 1.26–3.64, P = 0.005) of death. The results were robust after different degree of adjustment.

Conclusion

Certain amount of BF was not associated with increased risk of all-cause death in patients with CAD, even seems protective in those concomitant with LVH.

Introduction

Last 40 years have witnessed sharply rise of obesity prevalence at any age and gender around the world. In the concept of obesity transition, China has been classified into stage 2, which is characterized by a significant of increase of obesity prevalence in adults surpassing that among children, and a narrowing distinction between sexes [1]. In 2012, obesity prevalence in Chinese residents aged over 18 years old is 11.9%. About 13.5% of cardiovascular deaths were attributable to high body mass index in 2017; furthermore, the direct economic burden of overweight and obesity rose to 90.768 billion yuan (RMB), which is accounted for 4.5% of total health expenditure of China in 2010 [2]. Obesity, itself or concomitant with other comorbidities, contribute to a higher risk of incident coronary artery disease [3]. Cardiac remodeling and functional changes are also prevailing phenomena in obese individuals. A meta-analysis showed that the prevalence of left ventricular hypertrophy (LVH) in obese individuals was 56%, ranging from 20–85% according to different criteria of LVH [4]. In patients with coronary artery stenosis, LVH was associated with the presence of myocardial ischemia and the extent of involvement independent of traditional cardiovascular risk factors [5].

With the deepening of the research in heart failure with preserved ejection fraction, increasing weight has been given to the impact of obesity and LVH on cardiovascular system. Aslam et al. demonstrated that the reaction of ventricular sarcomere contractility to increased calcium stimulation in severe obese patients was substantially depressed compared to that in patients with primarily LVH [6]. Subclinical LV systolic and relaxation dysfunction were also observed in obese individuals; besides, a superposition effect of LVH and obesity on regional LV dysfunction has been observed [7]. Nevertheless, little is known about the interaction effect of obesity and LVH on the prognosis of patients with coronary

artery disease. In the study, we investigated the relationship of body fat and left ventricular hypertrophy with the risk of all-cause death in patients with coronary artery disease.

Methods

Study population

The study population was from the coronary artery disease database of West China Hospital, Sichuan University. In brief, West China Hospital CAD database is a large prospective registry study designed to explore risk factors, early warnings, risk stratification and management of patients with CAD (ChiCTR-OOC-17010433). The database was created in July 2008 and is ongoing to enroll all patients who have undergone invasive coronary angiography at West China Hospital. The information collected includes demographic data, cardiovascular risk factors, laboratory data, ultrasound indicators, angiographic results, medication, revascularization and clinical outcomes. Informed consent was given to all enrolled patients in this study, and ethical approval was obtained from the local institution. The primary inclusion criteria for this study were angiographically proven of stenosis greater than 50 percent in at least one major epicardial coronary arteries. The exclusion criteria included patients who had contraindications to coronary angiography, patients who did not receive echocardiographic examination during hospitalization, patients who were lost during follow-up, patients who died within the first month of discharge, and patients who were followed up for less than 1 month.

Measurement of major exposure factors

The main exposure factors of interest in this study were percentage of body fat and left ventricular mass index. A formula based on body mass index, sex and age (Clínica Universidad de Navarra-Body Adiposity Estimator) was used to calculate body fat percentage [8]. Height and weight are measured by a trained nurse at admission. BMI was the ratio of body weight to the square of height. The study defined higher body fat as the percentage of body fat greater than the 75th percentile of included male or female patients. During the hospital stay, the patient underwent a comprehensive transthoracic echocardiographic examination in accordance with guideline recommendations. From the parasternal long axis view, the left ventricular diameter was measured using M-type or 2D guidance. Left ventricular volume and left ventricular ejection fraction were measured using the two-plane Simpsons method. The left ventricular myocardial mass was calculated using the formula recommended by the American Society of Echocardiography, and it was normalized using the height of 2.7 to obtain the left ventricular myocardial mass index [9]. According to the guideline definition, LVMI greater than 44 in women and 48 in men is defined as left ventricular hypertrophy. According to body fat percentage and LVMI, patients were divided into four groups: group 1, lower body fat and no LVH; group 2, lower body fat and LVH; group 3, higher body fat and no LVH; group 4, higher body fat and LVH.

Data on potential confounders and modifiers

Demographic characteristics, cardiovascular risk factors, comorbidities, and medical history were collected by a questionnaire interview at admission or search in medical record. Data of blood pressure, heart rate, laboratory data, angiographic results, medications, and revascularization therapy were obtained from medical records.

Follow-up and study endpoint

The endpoint of the study was all-cause death. In the follow-up of this study, telephone follow-up, review of medical records, and outpatient visits were mainly adopted. The events were confirmed by death certificates or close relatives. Each patient was followed up from the discharge until either death occurrence or the last follow-up, depending on which came first.

Statistical analysis

Continuous data were presented as mean \pm SD or median with interquartile range, and categorical data were presented as number and percentage. One-way analysis of variance and χ^2 test were conducted to compare the baseline characteristics of study participants. We used Cox proportional risk models to examine the associations between body fat percentage, left ventricular hypertrophy and all-cause mortality. Different models were used to look at the effect of covariates on prognosis. Model 1 is the result of no correction. Model 2 is adjusted for age and sex. Model 3 was adjusted for age, sex, LVEF, and creatinine. Model 4 corrects age, sex, LVEF, creatinine, hypertension, diabetes, current smoking, cholesterol, and left main or three-vessel disease. All analyses were performed using SPSS. P value < 0.05 on both sides indicated statistical difference.

Results

Of the 3686 patients enrolled during July 2008 and Sep 2012, 386 patients lost to follow-up, 1003 without echocardiographic results, 54 followed up less than 1 month or died during the first months were excluded.

Finally, our analyses were limited to 2243 patients in accordance to our inclusion criteria.

Of those, 956 were in group 1 (lower body fat and no LVH), 727 in group 2 (lower body fat and LVH), 242 in group 3 (higher body fat and no LVH), and 318 in group 4 (higher body fat and LVH).

As shown in Table 1, there were significant differences between different groups. Patients with higher body fat were older, had lower percentage of current smoker, and had higher body mass index. On the other hand, patients with LVH were more female, were more likely to be concomitant with cardiovascular risk factors (hypertension, diabetes, higher levels of serum cholesterol, glucose, creatinine, had lower levels of hemoglobin), and had higher admission blood pressure, heart rate, and lower LVEF; they also had higher possibility to be prescribed with ACE inhibitors, were more likely to have left main or three-vessel disease and need more stents to be implanted.

Table 1
Baseline characteristics of included patients across categories based on body fat percentage and presence of LHV

Characterisitc	All(N = 2243)	Group1(N = 956)	Group2(N = 727)	Group3(N = 242)	Group4(N = 318)	P-value
Demograohics and history						
Age (years), mean(SD)	64.6(10.5)	63.0(10.9)	64.5(10.1)	66.9(9.1)	67.9(9.6)	< 0.001
Male, n(%)	1778(79.3)	820(85.8)	514(70.7)	217(89.7)	227(71.4)	< 0.001
Hypertension, n(%)	1265(56.4)	430(45.0)	455(62.6)	146(60.3)	234(73.6)	< 0.001
Diabetes, n(%)	506(22.6)	168(17.6)	187(25.7)	58(24.0)	93(29.2)	< 0.001
Current smoker, n(%)	640(28.5)	325(34.0)	195(26.8)	61(25.2)	59(18.6)	< 0.001
Coronary artery disease subtypes						0.344
STEMI	254(11.3)	100(10.5)	95(13.1)	27(11.2)	32(10.1)	
NSTEMI	143(6.4)	53(5.5)	52(7.2)	13(5.4)	25(7.9)	
Unstable angina	1178(52.5)	498(52.1)	371(51.0)	134(55.4)	175(55.0)	
Stable coronary artery disease	668(29.8)	305(31.9)	209(28.7)	68(28.1)	86(27.0)	
Clinical measurements						
Body mass index (kg/m ²), mean(SD)	24.1(2.9)	22.8(2.2)	23.3(1.9)	27.4(1.8)	27.8(2.2)	< 0.001
Body fat percentage (%)	28.1(6.3)	25.4(5.1)	28.1(6.3)	31.2(4.1)	33.9(6.0)	< 0.001
Systolic blood pressure, mean(SD)	130.9(21.0)	126.8(19.0)	133.6(22.4)	130.0(20.1)	137.7(21.8)	< 0.001
Diastolic blood pressure, mean(SD)	76.5(12.3)	74.9(11.3)	78.3(13.0)	75.8(12.2)	77.6(12.9)	< 0.001
Heart rate, mean(SD)	73.4(13.3)	72.3(13.0)	75.2(14.0)	71.2(11.6)	74.5(13.2)	< 0.001
Biochemical parameters						
Cholesterol(mmol/L),mean(SD)	4.1(1.1)	4.0(1.1)	4.2(1.2)	4.0(1.0)	4.1(1.1)	0.043
LDL cholesterol (mmol/L),mean(SD)	2.3(0.9)	2.3(0.9)	2.4(1.0)	2.3(0.8)	2.4(0.9)	0.075
Triglyceride(mmol/L),mean(SD)	1.7(1.2)	1.7(1.2)	1.7(1.2)	1.7(0.9)	1.9(1.1)	0.058
Glucose(mmol/L),mean(SD)	6.9(3.0)	6.4(2.5)	7.3(3.5)	7.0(3.1)	7.2(3.0)	< 0.001
Serum creatinine(umol/L),mean(SD)	94.3(53.5)	89.0(37.5)	97.5(67.6)	97.1(36.8)	100.4(66.2)	0.001

Characteristic	All(N = 2243)	Group1(N = 956)	Group2(N = 727)	Group3(N = 242)	Group4(N = 318)	P-value
Hemoglobin(mmol/L),mean(SD)	133.9(17.7)	135.9(16.4)	131.0(19.1)	136.7(17.4)	132.6(17.6)	< 0.001
Echocardiographic parameters						
LVMI	48.7(14.1)	38.4(5.8)	59.5(11.8)	40.0(5.5)	61.7(11.8)	< 0.001
Relative wall thickness	0.4(0.1)	0.4(0.1)	0.4(0.1)	0.4(0.1)	0.4(0.1)	< 0.001
LVEF, mean(SD)	60.6(11.3)	63.1(9.5)	56.8(12.6)	64.0(9.0)	59.4(11.9)	< 0.001
Medication and angiographic results						
Aspirin,n(%)	2111(94.7) (N = 2230)	899(95.0) (N = 946)	684(94.3) (N = 725)	227(93.8) (N = 242)	301(95.0) (N = 317)	0.848
Clopidogrel,n(%)	2051(92.0) (N = 2230)	876(92.6) (N = 946)	661(91.2) (N = 725)	220(90.9) (N = 242)	294(92.7) (N = 317)	0.624
Statins,n(%)	2049(91.9) (N = 2230)	870(92.0) (N = 946)	658(90.8) (N = 725)	228(94.2) (N = 242)	293(92.4) (N = 317)	0.372
ACE inhibitors/ARB,n(%)	1304(58.5) (N = 2230)	491(51.9) (N = 946)	463(63.9) (N = 725)	142(58.7) (N = 242)	208(65.6) (N = 317)	< 0.001
Beta-blockers,n(%)	1527(68.5) (N = 2230)	619(65.4) (N = 946)	514(70.9) (N = 725)	176(72.7) (N = 242)	218(68.8) (N = 317)	0.045
Left main and three-vessel disease,n(%)	666(29.7)	232(24.3)	242(33.3)	69(28.5)	123(38.7)	< 0.001
PCI,n(%)	1558(69.5)	675(70.6)	493(67.8)	169(69.8)	221(69.5)	0.673
Stents numbers, median(Q1-Q3)	2(1-2)	1(1-2)	2(1-3)	2(1-2)	2(1-2.5)	0.002
STEMI, ST-Segment Elevation Myocardial Infarction; NSTEMI, non-ST segment elevation myocardial infarction; LDL, low-density lipoprotein; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blockers; PCI, percutaneous coronary intervention.						

Over a median follow-up duration of 2.2 years, a total of 120 deaths occurred. Compared to patients with lower body fat and no LVH (24, 2.5%), those with higher body fat and LVH (26, 8.2%) showed the highest risk of death. Table 2 demonstrated the Cox model results with different degree of adjustment. The results of different adjusted models showed that patients with higher body fat and no LVH (group 3) had similar risk of death compared to the reference group (lower body fat and no LVH, group 1), while patients with lower body fat and LVH (group 2) had the highest risk of death, no matter adjusting for age and sex, other cardiovascular risk factors, cardiac function, or angiographic proven complex lesions. For the fully adjusted model, patients with lower body fat and LVH were more than 2 times likely to suffer from death compared to reference group (HR 2.15, 95%CI 1.26–3.64, P = 0.005), while there were no significant differences of risk of death between those with higher body fat and LVH and reference group (HR 1.83, 95%CI 1.00-3.38, P = 0.054) (Fig. 1).

Table 2
Number of death events across groups and association of body fat, LVH and all-cause death with different model adjustment

Outcome	Outcome number and rates by subgroups				
	All(n = 2243) (event rate)	Group1(n = 956) (event rate)	Group2(n = 727) (event rate)	Group3(n = 242) (event rate)	Group4(n = 318) (event rate)
All-cause death	120(5.3)	24(2.5)	57(7.8)	13(5.4)	26(8.2)
Unadjusted hazard ratio(95%CI), P-value		Reference	3.19(1.98–5.15), P < 0.001	2.10(1.07–4.13), P = 0.031	3.16(1.81–5.50), P < 0.001
Adjusted for age and sex		Reference	3.04(1.88–4.93), P < 0.001	1.57(0.80–3.10), P = 0.191	2.44(1.39–4.27), P = 0.002
Adjusted for age, sex, LVEF and creatinine		Reference	2.08(1.26–3.43), P = 0.004	1.56(0.79–3.08), P = 0.198	1.86(1.05–3.30), P = 0.033
Adjusted for age, sex,LVEF,creatinine, hypertension, diabetes, current smoking, cholesterol, left main or three-vessel disease		Reference	2.15(1.26–3.64), P = 0.005	1.69(0.85–3.38), P = 0.136	1.83(1.00–3.38), P = 0.054

Discussion

The primary findings of the present study are: firstly, patients with higher body fat but without LVH have a similar risk of all-cause death when compared to patients with lower body fat and without LVH, and have a more favorable prognosis than patients with LVH and lower body fat; secondly, CAD patients with LVH and lower body fat had the worst outcome among different groups, even compared to those with both LVH and higher body fat.

Our study demonstrated that patients with higher body fat were more likely to suffer from death when compared to their counterparts with lower body fat and without LVH; nevertheless, the possible negative association disappeared after adjusting for age and other confounders. For patients whose left ventricular is hypertrophic due to diverse causes, it seemed that higher body fat was correlated with lower risk of mortality. Intuitively, physicians would expect the likelihood of CAD to increase with BMI, but in fact is not the case, and the severity of obesity may be inversely correlated with poor outcomes in patients with suspected myocardial ischemia [10]. In an observational study of median follow-up duration of 68 months, obesity was associated with a decreased risk of mortality in patients with dipyridamole induced ischemic regional wall motion abnormalities or abnormal coronary flow velocity reserve (HR 0.58, 95% CI 0.40–0.84; p = 0.003) [11]. A registry study from Asian population revealed an inverse relationship between BMI and 3-year incident rate of death and myocardial infarction [12]. In a Chinese cohort of 8943 patients with angiographically confirmed triple-vessel disease, overweight and mild obesity (adjusted HR 0.83, 95% CI 0.69–1.00) was correlated with a lower odd of mortality with a median follow-up of over 7 years. What is intriguing is that interaction effect was observed between treatment strategies and BMI, that is, severe obesity is associated with increased risk of mortality in patients undergoing revascularization but is correlated with decreased risk of death in patients receiving medical treatment [13]. In a prospective multicenter study, patients who had undergone percutaneous coronary intervention were divided into three groups according to the changes of BMI. During a follow up of 4 years, patients with reduced BMI have a significantly higher risk of incident major adverse cardiac events than those with maintained or increased BMI, even after adjusting for confounders [14]. BMI fluctuation and decrease were also associated with cardiovascular death in patients with

myocardial infarction and left ventricular dysfunction or heart failure [15]. The U-shaped relationship between obesity and cardiovascular outcomes in patients with CAD has been confirmed in meta-analyses [16]. Pirlet et al. investigated the effect of bariatric surgery in obese patients with a history of myocardial revascularization. During a follow up of near 9 years, although the rate of death and major adverse cardio-cerebral events was significantly lower in patients underwent bariatric surgery than their counterparts not underwent surgery, the effect was driven by non-cardiac mortality but not all-cause or cardiovascular death [17]. Accumulating evidence suggested that certain amount of body fat, at least was not detrimental to patients with CAD.

A wealth supporting evidence confirmed that left ventricular hypertrophy was associated with adverse outcomes in different populations [18]. Subjects with obesity or higher BMI are more prone to have an increased left ventricular mass. Besides, it has been demonstrated that pericoronary adipose tissue attenuation was independently correlated with LVMI [19]. Our study showed that patients with higher body fat had a better prognosis than those with LVH. The findings were in contradiction with the experimental results which showed that myocardial contractility was more depressed in severe obese patients than those with LVH [6]. However, the present findings are partly supported by the phenomena of "obesity paradox". Although LVH is one of the strongest prognostic factor in patients with CAD and has the equivalent effect as LVEF, effective therapies targeting for regression of LVH are numbered and yielded limited effect [20]. The results of the study remind us that for the management of patients with CAD, more efforts are required to prevent LVH or regress it. In patients with concomitant with LVH and higher body fat, the target which should be pursued is also regression of LVH. In that sense, accompanying disease or dysfunction, such as hypertension, diabetes, insulin resistance, and systematic inflammation should be focused on beyond obesity itself.

It is not quite clear why patients with CAD and higher BF have no worse prognosis than those with lower BF, and even have a better outcome than patients with lower BF when they are concomitant with LVH. The following reasons may account for these phenomena to a certain extent. First of all, greater metabolic reserves in patients with higher body fat enable them to overcome from acute phase of CAD or subsequent LV dysfunction [21]. Secondly, BMI of patients with higher body fat in our study is about 27 ~ 28, which is intermediate between traditional definition of overweight and obesity; however, the body fat range may be ideal in the patients with CAD when considering the age, ethnicity and the presence of established disease. With many biological benefit, increased weight and body fat is essential in aging and disease states, for instance, those with LVH and reduced LVEF [22]. Lastly, patients with higher body fat have an unhealthy phenotype which may promote them to pursue aggressive control of a variety of risk factors, especially when they are hospitalized for CAD.

Limitations

First of all, body fat distribution was unavailable in the present study. Visceral adipose tissue (VAT) may have a superior predictive effect for progression of CAD than subcutaneous adipose tissue, while the assessment of demands more advanced equipments such as CT scan. Secondly, BF value in the study was calculated by formulas but not measured directly by dual-energy X-ray measurements or bioelectrical impedance techniques. Thirdly, because there was lack of generally acknowledged cutoff values for define obesity using body fat value, we used 75 quantile arbitrarily to divided investigated subjects into different groups. However, the optimal value of body fat may be varied on the basis of age, sex, and energy demand. Lastly, this study did not track the body measurement index and echocardiographic results of patients after discharge, and it was less likely to know how the proportion of patients in the defined groups changed, furthermore, it was unclear what effect this change had on the endpoints.

Conclusions

Certain amount of BF was not associated with increased risk of all-cause death in patients with CAD, while LVH was a more powerful unfavorable prognostic factor than higher BF. CAD patients who had LVH and lower BF had the worst outcome.

Abbreviations

LVH: left ventricular hypertrophy; LV: left ventricular. CAD: coronary artery disease; VAT: visceral adipose tissue; BMI: body mass index; LVMI: left ventricular mass index; LVEF: left ventricular ejection fraction.

Declarations

Acknowledgements

Not applicable.

Authors' contributions

BTH and LY designed the study, collected the data, and drafted the article. BSY designed the study, analyzed the data, and drafted the article. FYH, QFX and XBP collected the data and revised the article. YP and MC designed the study, drafted the article, and revised it. All authors read and approved the final manuscript.

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Funding

Dr Huang reported a grant from the Key Research and Development Projects of Science & Technology Department of Sichuan Province (2019YFS0351).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. **Ethics approval and consent to participate**

The study protocol was approved by the institutional review boards of West China Hospital, Sichuan University, an institutional ethics committee. All subjects provided written informed consent before enrolment.

Consent for publication

All authors gave their consent for publication of this manuscript.

Competing interests

The authors declare that they have no competing interests.

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Figures

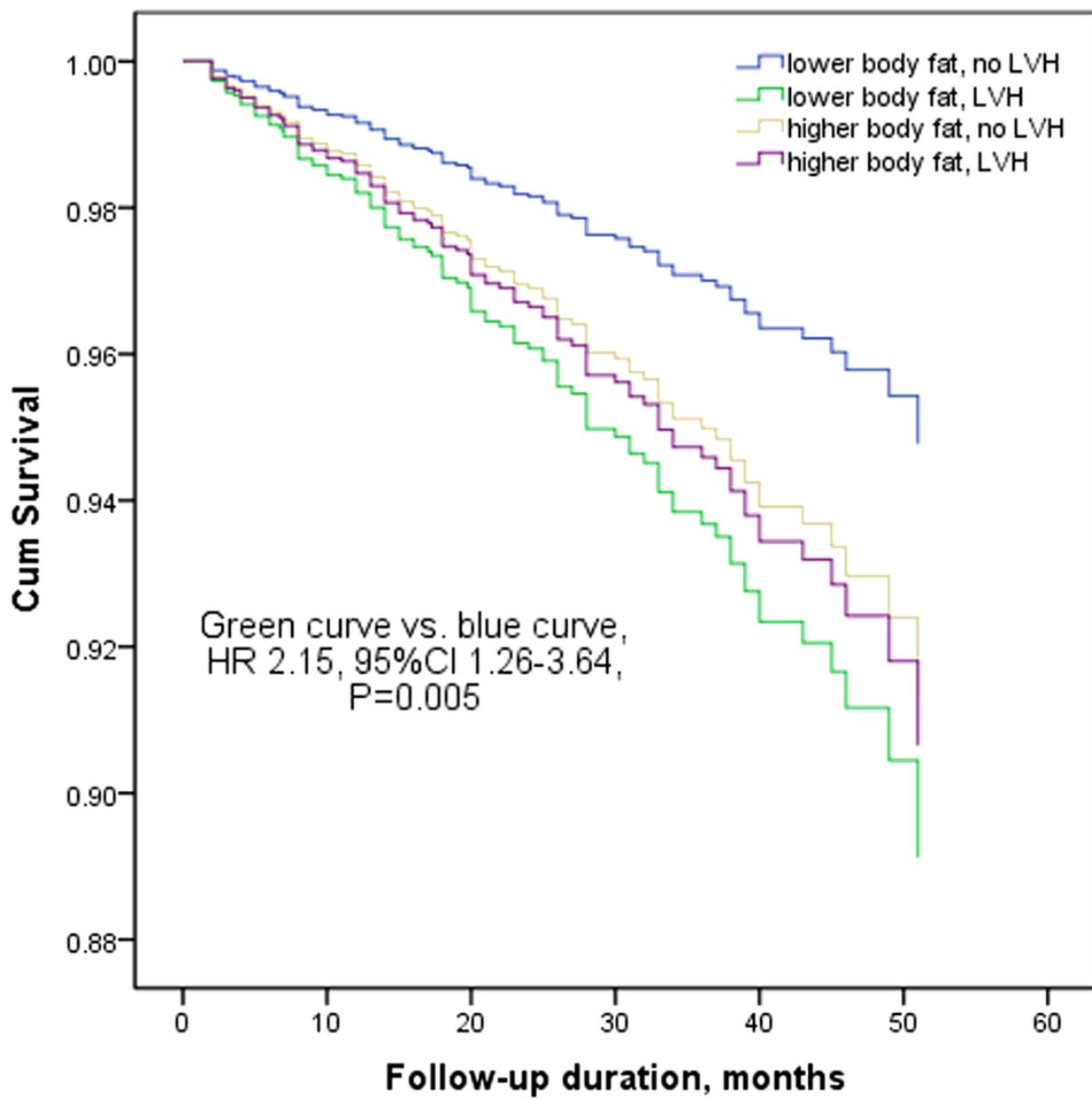


Figure 1

Cumulative survival according to body fat percentage and presence of LVH.