Clinical significance of overweight in patients with hypertrophic cardiomyopathy
A retrospective cohort study

Ziwei Chen, MD †, Biao Xu, MD *

Abstract
Hypertrophic cardiomyopathy (HCM) is a common genetic heart disease with varying clinical outcomes and it is important to identify new predictors of adverse events and survival in HCM patients. Overweight may independently predict the clinical outcomes of HCM patients. This was a retrospective study. Two hundred six HCM patients were compared classified by the normal group (body mass index < 25 kg/m²) and the overweight group (body mass index ≥ 25 kg/m²). We compared major adverse cardiovascular and cerebral events and secondary endpoints between 2 groups. By Cox analysis, we determined whether overweight was an independent predictor of MACCE in HCM patients. Finally, we also explored the prognostic value of overweight on all-cause death in HCM cohorts using Kaplan–Meier analysis.

Overweight patients were associated with more heart failure (HF) rehospitalization in HCM patients (51.3% vs 27.5%, P = .001). Overweight was an independent determinant of MACCE in HCM patients (heart rate = 3.40, 95% confidence interval: 1.79–6.61, P < .001), mainly attributed to HF rehospitalization (heart rate = 3.44, 95% confidence interval: 1.64–6.72, P < .001). However, a prognostic effect of overweight on overall survival was not observed by Kaplan–Meier analysis (P = .23). These results provide the evidence that overweight could predict the presence of MACCE, especially HF rehospitalization, in HCM patients.

Abbreviations: BMI = body mass index, CAD = coronary artery disease, CHF = chronic heart failure, CI = confidence interval, HCM = hypertrophic cardiomyopathy, HF = heart failure, HR = heart rate, KM = Kaplan–Meier, MACCE = major adverse cardiovascular and cerebral events, SCD = sudden cardiac death.

Keywords: heart failure rehospitalization, hypertrophic cardiomyopathy, overweight

1. Introduction
Hypertrophic cardiomyopathy (HCM) is a common genetic heart disease, with a incidence of more than 1/500. [1] The reported annual mortality is approximately 0.5% in population-based cohorts. [2] It is well-known that HCM arise from mutations in genes encoding proteins of the cardiac sarcomere, mainly including beta-myosin heavy chain and myosin-binding protein C. [3] The clinical outcomes of HCM patients varied from asymptomatic to diastolic dysfunction, progressive heart failure, atrial fibrillation, stroke, and sudden cardiac death (SCD). [4] However, genetic causes could not explain the prognosis of all HCM. [5]

Long-term efforts have focused on determining the prognostic factors of HCM, such as age, family history, diabetes, right ventricular systolic dysfunction, non-sustained ventricular tachycardia, obstruction, and so on. [6–8] Obesity is also associated with the phenotype and clinical progression of HCM patients, which is independently related to left ventricular mass, and progressive heart failure. [9] However, the effect of overweight on HCM patients was lacking.

Our study is to describe the presence and prognostic effect of overweight on major adverse cardiovascular and cerebral events (MACCE) of HCM patients. Besides, we also investigated whether overweight predicted poor survival of HCM.

2. Method
2.1. Study population
Patients who were admitted for HCM in the department of cardiology at Nanjing Drum Tower Hospital from January 2010 to December 2015 were retrospectively recruited in this study. Two hundred six patients with complete follow-up data by June 2018 were enrolled in this study. The criteria of a diagnosis of
HCM was in accordance with 2014 European Society of Cardiology guidelines on diagnosis and management of HCM.\[10\] It was defined as unexplained left ventricular hypertrophy with a maximal wall thickness above 15mm showed by any cardiac imaging, such as echocardiography, cardiac magnetic resonance, or computed tomography. All patients with cardiac hypertrophy caused by physiologic cardiac hypertrophy, rheumatic heart disease, mitral valve disease, amyloidosis, and Fabry disease were excluded. After a median follow-up of 22 (12–36) months, the primary endpoint was MACCE, including cardiac death, heart failure (HF) rehospitalization, and stroke. This retrospective study was approved by Nanjing Drum Tower Review Board (No. 2019AE01062).

2.2. Cardiac evaluation

Electrocardiographic measurements were performed with commercially available instruments. Echocardiographic data included left ventricular end diastolic diameter, left ventricular end systolic diameter, end diastolic ventricular septal thickness, left ventricular posterior wall end diastolic thickness, aortic dimension, left ventricular ejection fraction, and E/A ratio. Left ventricular outflow obstruction was identified by a peak instantaneous outflow gradient \( \geq 30 \text{mmHg} \) occurring under basal conditions. Left ventricular systolic dysfunction was defined as left ventricular ejection fraction \( < 50\% \), and left ventricular diastolic dysfunction as E/A \( < 1 \). Left ventricular mass and left ventricular mass index were calculated based on the Devereux method.\[11\]

2.3. Statistical analysis

Continuous variables were expressed as mean±Standard deviation, and categorical variables were expressed as a proportion. For the comparison of normally distributed variables, we employed Student \( t \) test. Chi-square test was utilized to compare categorical variables; Fisher exact test was employed when 1 or more cells in the comparison table had \( \leq 5\). The dependence of variables associated with increased MACCE were assessed by Cox regression. Survival analysis was described by using the Kaplan–Meier (KM) survival analysis method with a log-rank test. \( P \) values are 2-sided and considered significant when \( P < .05 \). The statistical analysis was carried out with the use of SPSS 12.0 software (Chicago, IL).

3. Result

3.1. Baseline features of HCM patients in relation to body mass index

The 206 HCM patients had an average body mass index (BMI) of 24.7±3.3 kg/m\(^2\). Among them, 91 (44.2\%) patients were in the normal group (BMI \(< 25\text{kg/m}^2\) ) with average 21.8±1.7 kg/m\(^2\) and 115 (55.8\%) patients were in the overweight group (BMI \( \geq 25\text{kg/m}^2 \)) with average 26.9±2.5 kg/m\(^2\), respectively (Table 1). Demographic, clinical, and echocardiography characteristics of the 2 groups are shown in Table 1. There were no significant differences in age, gender, smoking, and hypertension between the groups. In addition, we did not observe statistical differences in the prevalence of comorbidities, including atrial fibrillation, coronary artery disease (CAD), and chronic heart failure (CHF) >1 years, and cardiovascular medications between 2 groups. There was a trend for bigger left ventricular end systolic diameter \((P = .027)\), left ventricular end diastolic diameter \((P = .016)\), and aortic dimension \((P < .001)\) while not in the other echocardiography data in overweight patients.

With respect to clinical outcomes in HCM patients, there were in total 86 MACCE, including 17 cardiac deaths, 6 strokes, and 84 HF rehospitalization for an average of 53.3-month follow-up. A significant difference in the prevalence of MACCE was observed between the normal group and the overweight group (28.6\% vs 52.2\%, \( P = .001 \)), which was mainly attributed to the HF rehospitalization (27.5\% vs 51.3\%, \( P = .001 \)). However, the occurrence of SCD, as a common endpoint in HCM, showed no significant difference \((P = .813)\) in the overweight group than the normal group.

3.2. Associations between overweight and HCM clinical outcomes

To evaluate whether BMI was a predictor of clinical outcomes in HCM patients, we constructed univariable and multivariable logistic regression models (Table 2). As a continuous variable, BMI was significantly associated with MACCE (heart rate (HR) = 1.14, 95\% confidence interval (CI): 1.04 vs 1.24, \( P = .004 \), which was attributed to HF rehospitalization (HR = 1.14, 95\% CI: 1.04–1.24, \( P = .005 \)). After adjusted for sex, age, smoking, family history, hypertension, hyperlipidemia, diabetes mellitus, percutaneous coronary intervention, atrial fibrillation, CAD, CHF >1 years, and use of diuretics, BMI was also independently associated with MACCE (HR = 1.16, 95\% CI: 1.06–1.31, \( P = .005 \), particular with HF rehospitalization (HR = 1.13, 95\% CI: 1.05–1.28, \( P = .009 \)).

As a dichotomous variable (Table 3), overweight HCM patients had a 2.73-fold higher risk of developing MACCE (HR = 2.73, 95\% CI: 1.52–4.89, \( P = .001 \)), specifically a 2.78-time higher risk of developing HF rehospitalization (HR = 2.78, 95\% CI: 1.55–5.00, \( P = .001 \)), compared with normal-weight patients. After adjusted for cardiovascular risk factors and comorbidity, the prognostic effect of overweight on MACCE (HR = 3.40, 95\% CI: 1.79–6.61, \( P < .001 \)), and HF rehospitalization (HR = 3.44, 95\% CI: 1.64–7.62, \( P < .001 \)) still existed. With regard to other clinical outcomes, there was no significant difference between 2 groups.

3.3. Prognostic effect of overweight on overall survival

A KM model was constructed to assess the prognostic value of overweight on overall survival in HCM patients. From the survival plot (Fig. 1), we could find that overweight patients had a more percentage of all-cause death, especially in the long term. However, the prognostic effect of overweight on HCM was not statistical different \((P = .23)\).

4. Discussion

We reported that overweight was independently associated with poor outcomes in HCM patients using multivariate logistic regression models. Particularly, overweight was a predictor of HF rehospitalization in HCM patients.

Both as a dichotomous variable and a continues variable, greater BMI was associated with worsen clinical outcomes, which was in accordance with previous reports.\[9,12\] In univariate
Echocardiography

| Parameter                  | Overall | Normal, BMI < 25 kg/m² | Overweight, BMI ≥ 25 kg/m² | P value |
|----------------------------|---------|------------------------|-----------------------------|---------|
| LVEF, %                    | 59.0 ± 14.9 | 57.8 ± 6.3             | 60.0 ± 19.2                 | .292    |
| IVSTd, cm                  | 1.52 ± 0.43 | 1.50 ± 0.44           | 1.54 ± 0.43                 | .564    |
| LVEDd, cm                  | 4.88 ± 0.52 | 4.78 ± 0.47           | 4.96 ± 0.55                 | .016    |
| LVESd, cm                  | 3.35 ± 0.42 | 3.28 ± 0.35           | 3.41 ± 0.45                 | .027    |
| LVPWTd, cm                 | 1.17 ± 0.29 | 1.17 ± 0.23           | 1.16 ± 0.33                 | .907    |
| AoD, cm                    | 3.21 ± 0.30 | 3.12 ± 0.28           | 3.28 ± 0.29                 | <.001   |
| PA, cm                     | 0.92 ± 0.18 | 0.91 ± 0.19           | 0.93 ± 0.17                 | .508    |
| E/A ratio                  | 0.98 ± 0.39 | 0.95 ± 0.33           | 1.00 ± 0.43                 | .283    |
| Ao, cm/s                   | 1.47 ± 0.50 | 1.55 ± 0.63           | 1.40 ± 0.36                 | .699    |
| LAD, cm                    | 4.37 ± 0.56 | 4.31 ± 0.60           | 4.42 ± 0.53                 | .151    |
| Max thickening, cm         | 1.79 ± 0.34 | 1.79 ± 0.36           | 1.80 ± 0.33                 | .835    |
| Obstruction                | 49 (23.8)  | 20 (22.0)             | 29 (25.2)                   | .588    |
| LVM, g                     | 319.8 ± 102.9 | 308.9 ± 94.4       | 328.4 ± 108.7               | .177    |
| LVMI, g/m²                 | 183.2 ± 56.1 | 188.8 ± 57.4         | 178.7 ± 54.8                | .198    |

Clinical outcomes

| Parameter                  | Overall | Normal, BMI < 25 kg/m² | Overweight, BMI ≥ 25 kg/m² | P value |
|----------------------------|---------|------------------------|-----------------------------|---------|
| MACCE                      | 86 (41.7) | 26 (28.6)             | 60 (52.2)                   | .001    |
| Cardiac death              | 17 (8.3)  | 5 (5.5)                | 12 (10.4)                   | .201    |
| Stroke                     | 6 (2.9)   | 1 (1.1)                | 5 (4.3)                     | .168    |
| HF-rehospitalization       | 84 (40.8) | 25 (27.5)             | 59 (51.3)                   | .001    |
| SCD                        | 4 (1.9)   | 2 (2.2)                | 2 (1.7)                     | .813    |

Regression, we observed that overweight patients had a 2.78-time higher risk of developing HF rehospitalization compared with normal-weight patients. After adjusted for other cardiovascular risk factors, including sex, age, smoking, family history, hypertension, atrial fibrillation, CAD, and CHF ≥ 1 years, overweight was independently associated with HF rehospitalization (HR 3.44, 95% CI 1.64–6.72; P < 0.001), which may be explained by less exercise tolerance in overweight patients reported by Canepa et al.[12] Similarly, Olivotto et al.[9] revealed that obese patients had a 3.6-fold risk of developing New York Heart Association III to IV symptoms. And no difference was observed in all-cause mortality among the normal groups, pre-obese groups, and obese group. KM analysis also showed no significant prognostic effect. Even though, we could find more all-cause death in overweight patients, and the difference became more obvious in the long term. So, a study with more population.
and longer follow-up was needed to verify the prognostic effect of overweight on overall survival. Obesity was an important predictor of HF in the general population.\(^{13,14}\) The underlying pathophysiology could be related to increased oxygen overload, sympathetic and neuro-hormonal activation, and oxidative stress, contributing to reduced cardiac efficiency.\(^{15}\) Our data also suggested that excessive body weight in HCM patients may increase the risk of HF rehospitalization, potentially forming a vicious cycle where overweight cause a sedentary lifestyle, which conversely increased body weight. However, no increased mortality was observed in overweight patients with HCM, which may be attributed to “obesity paradox”, a phenomenon that BMI predicted favorable outcomes in patients with CHF.\(^{16}\)

Several limitations need to be noted. Although there was obvious difference in HF rehospitalization of HCM patients between 2 groups, the exact causes of adverse cardiac events remained unknown. In addition, only a minority of HCM patients developed SCD, so it remained to be determined if overweight increased the risk of SCD in HCM patients in a large sample. Thirdly, cardiac magnetic resonance data were lacking, which may facilitate accurate diagnosis of HCM compared to echocardiography. Finally, a prospective and multicenter study should be carried out to differentiate overweight, obese, and normal weight patients and explore the relation between obesity and the development of HF.

## 5. Conclusions

We demonstrated that overweight, or a large BMI, was independently associated with more MACCE in HCM patients, mainly due to more HF rehospitalization. However, overweight may not predict poor overall survival of HCM patients.

## Author contributions

Conceptualization: Ziwei Chen, Biao Xu.
Data curation: Ziwei Chen.
Formal analysis: Ziwei Chen.
Funding acquisition: Biao Xu.
Writing – review & editing: Biao Xu.

## References

[1] Marian AJ, Braunwald E. Hypertrophic cardiomyopathy: genetics, pathogenesis, clinical manifestations, diagnosis, and therapy. Circ Res 2017;121:749–70.
[2] Maron BJ. Clinical course and management of hypertrophic cardiomyopathy. N Engl J Med 2018;379:633–68.
[3] Watkins H, Ashrafian H, Redwood C. Inherited cardiomyopathies. N Engl J Med 2011;364:1643–56.
[4] Maron BJ, Olivotto I, Spirito P, et al. Epidemiology of hypertrophic cardiomyopathy-related death: revisited in a large non-referral-based patient population. Circulation 2000;102:858–64.
[5] Olivotto I, Cecchi F, Poggesi C, Yacoub MH. Patterns of disease progression in hypertrophic cardiomyopathy: an individualized approach to clinical staging. Circ Heart Fail 2012;5:535–46.
[6] Shah JP, Yang Y, Chen S, et al. Prevalence and prognostic significance of right ventricular dysfunction in patients with hypertrophic cardiomyopathy. Am J Cardiol 2018;122:1932–8.

[7] Wasserstrum Y, Barriales-Villa R, Fernandez-Fernandez X, et al. The impact of diabetes mellitus on the clinical phenotype of hypertrophic cardiomyopathy. Eur Heart J 2019;40:1671–7.

[8] Maron BJ, Maron MS, Semsarian C. Genetics of hypertrophic cardiomyopathy after 20 years: clinical perspectives. J Am Coll Cardiol 2012;60:705–15.

[9] Olivotto I, Maron BJ, Tomberli B, et al. Obesity and its association to phenotype and clinical course in hypertrophic cardiomyopathy. J Am Coll Cardiol 2013;62:449–57.

[10] Elliott PM, Anastasakis A, et al. Authors/Task Force. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J 2014;35:2733–79.

[11] Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. Circulation 1977;55:613–8.

[12] Canepa M, Sorensen LL, Pozios I, et al. Comparison of clinical presentation, left ventricular morphology, hemodynamics, and exercise tolerance in obese versus nonobese patients with hypertrophic cardiomyopathy. Am J Cardiol 2013;112:1182–9.

[13] Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. JAMA 2013;309:71–82.

[14] Kenchaiah S, Evans JC, Levy D, et al. Obesity and the risk of heart failure. N Engl J Med 2002;347:305–13.

[15] Oreopoulos A, Padwal R, Kalantar-Zadeh K, Fonarow GC, Norris CM, McAlister FA. Body mass index and mortality in heart failure: a meta-analysis. Am Heart J 2008;156:13–22.

[16] Tourki B, Halade GV. The failing of the obesity paradox in the failing heart. Am J Physiol Heart Circ Physiol 2018;315:H1353–5.