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ORIGINAL RESEARCH

RoMa: A Cardiopulmonary Exercise Testing Based Risk Tool in Hypertrophic Cardiomyopathy

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BACKGROUND: The RoMa classification, based on peak heart rate and oxygen pulse derived from cardiopulmonary exercise testing, was recently proposed to stratify patients with hypertrophic cardiomyopathy by physiological reserve during exercise. We aimed to externally validate RoMa in an independent multicenter cohort with hypertrophic cardiomyopathy and assess its association with long-term clinical outcomes.

METHODS: In this retrospective multicenter cohort study patients with hypertrophic cardiomyopathy, undergoing cardiopulmonary exercise testing, were consecutively enrolled. Patients were enrolled regardless of left ventricular outflow tract obstruction and were naïve to disease-specific therapy (eg, mavacamten). Patients were categorized into RoMa I to IV based on percentage of predicted heart rate and oxygen pulse. The primary end point was a composite of all-cause and cardiovascular death, sudden cardiac death, or aborted sudden cardiac death, heart failure–related hospitalization, stroke, systemic embolism, surgical myectomy, and heart transplantation.

RESULTS: The study included 292 patients (age 51 [36–63] years, 70% male sex, 30% with obstructive left ventricular outflow tract). Functional capacity declined hierarchically across RoMa groups (peak oxygen uptake 29.2 to 17.9 mL/kg/min; *P*-trend <0.001). During follow-up (≈6 years), 68 composite events occurred. Kaplan–Meier analysis showed significant differences in event-free survival across groups (log-rank *P*=0.019). In multivariable analysis, RoMa II to IV compared with RoMa I were independently associated with higher hazard ratios (HRs) for the composite outcome (HRs, 3.89–5.37; all *P*<0.05), whereas genotype, LVEF <50%, male sex, and left ventricular outflow tract obstruction were not predictive.

CONCLUSIONS: The RoMa classification independently predicts long-term, clinically relevant outcomes in hypertrophic cardiomyopathy regardless of left ventricular outflow tract obstruction and may provide a novel approach to risk stratification.

Key Words: cardiopulmonary exercise testing ■ heart rate ■ hypertrophic cardiomyopathy ■ prognosis ■ stroke volume

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CLINICAL PERSPECTIVE

What Is New?

- The RoMa classification, derived from percentage of predicted peak heart rate and oxygen pulse, stratifies patients with hypertrophic cardiomyopathy into physiologically distinct exercise profiles using routine cardiopulmonary exercise testing data.

What Are the Clinical Implications?

- RoMa is associated with long-term outcomes and may offer additional mechanistic insight alongside established cardiopulmonary exercise testing parameters such as peak oxygen uptake and ventilation to carbon dioxide production slope.
- Because it requires no additional equipment or testing, RoMa can be readily integrated into clinical practice to refine patient risk stratification and guide therapy selection in hypertrophic cardiomyopathy.

Nonstandard Abbreviations and Acronyms

AT	anaerobic threshold
CPET	cardiopulmonary exercise testing
HCM	hypertrophic cardiomyopathy
LGE	late gadolinium enhancement
O_2 pulse	oxygen pulse
VE	minute ventilation
VE/VCO_2 slope	ventilation to carbon dioxide production slope
VCO_2	carbon dioxide production
VO_2	oxygen uptake

Hypertrophic cardiomyopathy (HCM) is a myocardial disease characterized by unexplained left ventricular (LV) hypertrophy and marked heterogeneity in clinical presentation, functional limitation, and prognosis.[1]

Cardiopulmonary exercise testing (CPET) has emerged as a robust tool to evaluate functional capacity and guide management in patients with HCM,[2,3] with metrics such as peak oxygen uptake (VO_2) and the minute ventilation to carbon dioxide production (VE/VCO_2) slope being widely used in clinical trials to assess disease burden and therapeutic efficacy.[4–8] Moreover, limitation of exercise performance due to chronotropic incompetence has been frequently observed in patients with HCM.[9]

Recently, a novel classification system, RoMa, was developed using percent (%) predicted peak heart rate (HR) and % predicted peak oxygen pulse (O_2-pulse) as noninvasive surrogates of chronotropic reserve and stroke volume (SV) reserve, respectively.[10] This stratification allows the categorization of patients with HCM into 4 physiologically distinct exercise profiles, each with differing degrees of hemodynamic limitation and clinical severity.

To allow widespread use of the RoMa classification in the clinical field, we aimed to validate the RoMa classification in a larger, independent cohort with HCM from a multicenter registry[11] and to analyze longitudinal outcome data to test whether the RoMa classification holds prognostic value beyond exercise-related, clinical, and imaging parameters.[12–15]

METHODS

This was a retrospective analysis of consecutively enrolled adult patients (≥18 years of age) with HCM, both obstructive and nonobstructive phenotypes, who underwent CPET as part of routine clinical evaluation. Patients were drawn from a previously published multicenter cohort.[11] HCM was defined as a maximal LV wall thickness ≥15 mm in the absence of another cardiac or systemic cause of hypertrophy. In genotype-positive individuals with LV outflow tract (LVOT) obstruction and corresponding ECG findings, a lower threshold of ≥13 mm was accepted. LV outflow tract obstruction was defined as LVOT gradient at rest ≥30 mm Hg. Patients were enrolled regardless of the presence of LVOT obstruction. Enrollment took place between January 2009 and October 2020 and therefore included patients naïve to disease-specific therapy (ie, mavacamten). Further inclusion and exclusion criteria have been previously published.[11] The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Considerations

The study received ethical approval from the Centro Cardiologico Monzino-IEO Ethic Committee (ID: R1540/21-CCM 1629), with all procedures adhering to the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all patients before study enrollment.

Exercise Testing

All CPETs were conducted using upright cycle ergometers and a patient-specific ramp protocol designed to reach maximal exertion within ~10 minutes. Tests were performed using validated metabolic carts (Quark PFT Cosmed, 229D Spectra metabolic cart, SensorMedics

and Vmax Encore System) with breath-by-breath gas exchange analysis.

Peak VO_2 was defined as the highest 30-second average during exercise and was expressed in mL/kg/min and as % of predicted values using Hansen–Wasserman equations.[16] The anaerobic threshold (AT) was determined using the V-slope method, supported by changes in ventilatory equivalents and end-tidal gas measurements.[17] Predicted maximal HR was calculated using the Fox formula (220–age), and % predicted HR was calculated accordingly.[18] O_2-pulse was computed as VO_2 divided by HR at peak and expressed as % of predicted.[19] The VE/VCO_2 slope was derived from the linear relationship between minute ventilation (VE) and carbon dioxide output (VCO_2) from rest to the respiratory compensation point.

RoMa Classification

The RoMa classification was calculated as previously described.[10] Patients were stratified using CPET derived thresholds for % predicted peak HR (HRpp ≥80%) and % predicted peak O_2-pulse (O_2pp ≥100%), resulting in 4 categories: RoMa I (HRpp ≥80% and O_2pp ≥100%), RoMa II (HRpp ≥80% and O_2pp <100%), RoMa III (HRpp <80% and O_2pp ≥100%), and RoMa IV (HRpp <80% and O_2pp <100%). Based on these cutoffs, patients were assigned to 1 of 4 RoMa groups.

Follow-Up and Outcomes

Patients were retrospectively followed for clinical outcomes via review of electronic health records and institutional databases. The primary end point was a composite of adverse events, including all-cause death, cardiovascular death, sudden cardiac death or aborted sudden cardiac death (ie, sudden cardiac arrest successfully reversed through resuscitation effort), heart failure related hospitalization, stroke or systemic embolism, surgical myectomy, and cardiac transplantation. In cases where patients experienced >1 qualifying event, only the first time point was counted toward the composite end point in the analysis. Survival time was calculated from the date of CPET to the first event or last available follow-up.

Statistical Analysis

Continuous variables were assessed for normality using the Shapiro–Wilk test within each RoMa group. Variables showing normal distribution across all groups were summarized as mean±SD and compared using 1-way ANOVA; otherwise, data were expressed as median (interquartile range) and compared using the Kruskal–Wallis test. Categorical variables were presented as counts and percentages and compared using chi-square or Fisher's exact tests, as appropriate.

Trend analyses across ordered RoMa categories were conducted using the Jonckheere–Terpstra test for continuous variables and the Cochran–Armitage test for binary categorical variables. Missing data were reported descriptively and handled using complete-case analysis.

Time-to-event analyses were performed using Kaplan–Meier curves, with event-free survival defined from the date of CPET to the first occurrence of the composite end point or last known follow-up. Log-rank tests were used for global and pairwise group comparisons. Survival curves included time point annotations at 3, 5, and 8 years.

Cox proportional hazards models were used to estimate hazard ratios (HRs) with 95% CIs. Univariable models assessed associations between individual covariates, including RoMa group, genotype, LV ejection fraction (LVEF) <50%, sex, late gadolinium enhancement (LGE), and LVOT obstruction with the composite outcome. Multivariable Cox modeling included the RoMa classification and clinically relevant covariates (genotype, sex, LVEF <50%, LVOT obstruction) that might be associated with prognosis.[12–15] RoMa group was entered as a categorical variable with RoMa I as reference. The proportional hazards assumption for the multivariable model was tested and not violated (*P* values >0.05 for all covariates in Schoenfeld residuals testing).

To directly compare prognostic performance, we additionally fitted a nested Cox model including RoMa, peak VO_2, and VE/VCO_2 slope (standardized per 1 SD) using identical complete cases. Model discrimination was quantified by Harrell's C-index (optimism-corrected via bootstrap, internal validation, B=200) and model fit by Akaike information criterion. Incremental prognostic value was assessed via likelihood-ratio χ^2 tests comparing reduced and full models (peak VO_2+VE/VCO_2 slope→peak VO_2+VE/VCO_2 slope+RoMa). The proportional hazards assumption was confirmed using Schoenfeld residuals (*P* values >0.05).

A 2-sided *P* value <0.05 was considered statistically significant. All analyses were performed using R (Version 4.4.2 – "Pile of Leaves", with the following statistical packages: survival, survminer, PMCMRplus, and DescTools alongside base R packges).

Efforts to Address Potential Sources of Bias

Consecutive patients were included to reduce selection bias, and data were extracted using standardized definitions and CPET protocols across centers. Confounding was addressed by adjusting for key clinical covariates in multivariable models, and missing data were handled by complete-case analysis.

RESULTS

The study population consisted of 292 patients with HCM. The median age was 51 (interquartile range, 36–63) years, and 205 patients (70%) were male. LVOT obstruction was present in 87 (30%) patients with HCM and genetic testing was positive for a pathological or likely pathological variant in 155 individuals (53%), 93 (32%) had a negative result, and in 44 (15%) patients, genetic result was unknown due to lack of consent. Patients had a median body mass index of 25.4 (interquartile range, 23.1–27.8) kg/m^2. Baseline echocardiography demonstrated a median maximal wall thickness of 19[17–22] mm and a median LVEF of 64% (interquartile range, 60%–65%), with LV end-diastolic diameter averaging 46±6 mm.

CPET revealed a median VO_2 peak of 22.6 (interquartile range, 17.6–27.9) mL/kg/min, corresponding to 78±19% predicted. The median VO_2 at the AT was 14.6 (interquartile range, 11.8–17.0) mL/kg/min, and the VE/VCO_2 slope was 27.5 (interquartile range, 24.8–31.2). Peak workload reached 120 (interquartile range, 85–158) Watt, and O_2-pulse at peak reached 12.9 (interquartile range, 10.5–15.6) mL/beat and HR at peak reached 135±27 bpm. Other baseline characteristics including further exercise metrics, echocardiography and medication can be seen in Table 1.

Validation of RoMa

The cohort of 292 patients was evenly distributed across RoMa categories: RoMa I (n=51), RoMa II (n=89), RoMa III (n=87), and RoMa IV (n=65), as displayed in Figure 1.

Across the RoMa spectrum, functional capacity gradually worsened. VO_2 peak declined progressively from 29.2 mL/kg/min in RoMa I to 17.9 mL/kg/min in RoMa IV (*P*-trend <0.001), with parallel reductions in VO_2 at AT (17.6 to 11.7 mL/kg/min, *P*-trend <0.001) and workload at both AT and peak. VO_2/work slope declined steadily (11.7 to 10.2 mL/min/W, *P*-trend <0.001), and VE/VCO_2 slope increased (25.9–28.7, *P*-trend=0.001), indicating worsening ventilatory efficiency. Respiratory reserve rose across groups (46%–56%, *P*-trend <0.001). HR at rest (*P*-trend <0.001), HR at AT (*P*-trend <0.001), and HR at peak (*P*-trend <0.001) were significantly different across groups, with lower values in higher RoMa classes. HR reserve showed a significant decreasing trend (*P*-trend <0.001) from 74±15 to 55±18 bpm from RoMa I to RoMa IV respectively.

No clear age trend was evident (*P*-trend >0.05) with RoMa III being the oldest (57.0 years) and RoMa IV youngest (46.7 years). Body mass index was highest in RoMa III (26.8 kg/m^2, *P*=0.003), but body surface area remained stable across groups. Maximal wall thickness showed a significant upward trend (18 mm in RoMa I to 22 mm in RoMa IV, *P*-trend <0.001), and from RoMa I to

Table 1. Characteristics of the Cohort With HCM

Overall cohort with HCM (N=292)	
Demographics	
Male sex, No. (%)	205 (70)
Age, y	51 (36–63)
Weight, kg	75 (67–85)
Height, cm	171±10
Body mass index, kg/m^2	25.4 (23.1–27.8)
Body surface area m^2	1.9±0.2
LV outflow tract obstruction, No. (%)	87 (30)
HCM genotype positive, No. (%)	155 (53)
Cardiopulmonary exercise testing	
Ramp protocol, Watt/min	12 (10–15)
Systolic blood pressure at rest, mm Hg	120 (108–130)
Diastolic blood pressure at rest, mm Hg	70 (70–80)
Heart rate at rest, bpm	70 (60–82)
VO_2 @ AT, mL/min	1108 (855–1352)
VO_2 @ AT, mL/kg/min	14.6 (11.8–17.0)
Heart rate @ AT, bpm	98 (86–112)
Workload @ AT*, Watt	63 (45–88)
O_2-pulse @ AT, mL/beat	11.0 (8.8–13.3)
VO_2 @ peak, mL/min	1781 (1229–2165)
VO_2 @ peak, mL/kg/min	22.6 (17.6–27.9)
VO_2 @ peak, % predicted	78±19
Heart rate @ peak, bpm	135±27
Heart rate reserve, bpm	63±21
Systolic blood pressure at peak, mm Hg	160 (140–190)
Diastolic blood pressure at peak, mm Hg	90 (80–100)
Workload @ peak, Watt	120 (85–158)
O_2-pulse @ peak, mL/beat	12.9 (10.5–15.6)
Ventilation to carbon dioxide production slope	27.5 (24.8–31.2)
VO_2/work slope, mL/min/W	10.9 (9.7–12.0)
Respiratory reserve, %	49 (39–58)
Peak ventilation, L/min	66 (49–80)
Respiratory quotient @ peak	1.1 (1.0–1.2)
O_2-pulse @ peak, % predicted	99 (84–114)
Heart rate @ peak, % predicted	77±13
Imaging at rest	
LV diastolic diameter (echocardiography), mm	46±6
LV systolic diameter (echocardiography), mm	30 (25–40)
Max wall thickness (echocardiography), mm	19 (17–22)
LV ejection fraction (echocardiography), %	64 (60–65)
Mitral insufficiency	
Not present, No. (%)	161 (55)
Mild, No. (%)	103 (35)
Moderate, No. (%)	24 (8)
Severe, No. (%)	2 (1)
Systolic anterior motion*, No. (%)	58 (20)
Late gadolinium enhancement (MRI)*, No. (%)	127 (43)

(*Continued*)

Table 1. Continued

Overall cohort with HCM (N=292)	
Heart rhythm and device therapy	
Atrial fibrillation, No. (%)	9 (3)
Stimulated QRS at presentation, No. (%)	6 (2)
Left BBB, No. (%)	9 (3)
Right BBB, No. (%)	9 (3)
Paced rhythm, No. (%)	20 (7)
Pacemaker, No. (%)	8 (3)
Implantable defibrillator, No. (%)	25 (9)
Cardiac resynchronization therapy, No. (%)	1 (<1)
Pharmacological and surgical therapy	
Previous myectomy, No. (%)	7 (2)
Beta blocker, No. (%)	185 (63)
Calcium channel blocker, No. (%)	28 (10)
Ivabradine, No. (%)	2 (1)
Antiarrhythmic medication, No. (%)	38 (13)
Diuretic therapy, No. (%)	43 (15)
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, No. (%)	92 (32)

This table summarizes demographic data, cardiopulmonary exercise testing metrics, echocardiographic and MRI-based structural assessments, rhythm and device therapies, and pharmacological or surgical treatments in the full study population (N=292). Continuous variables are reported as mean±SD or median (interquartile range), and categorical variables as counts with corresponding percentages.

AT indicates anaerobic threshold; BBB, bundle-branch block; HCM, hypertrophic cardiomyopathy; LV, left ventricular; MRI, magnetic resonance imaging; and VO_2, oxygen uptake.

*>30% but <50% missing.

RoMa IV (51%–79%, *P*-trend <0.001) LVOT obstruction showed a significant increasing trend. The prevalence of systolic anterior motion increased significantly from 8% in RoMa I to >30% in RoMa III (*P*-trend=0.001). However, the prevalence of mitral insufficiency and LGE enhancement was similar across groups.

Device therapy and arrhythmia burden rose in higher RoMa classes. Implantable cardioverter-defibrillator implantation was significantly more prevalent in RoMa IV (20%) compared with none in RoMa I (*P*-trend <0.001). Beta-blocker use increased across the spectrum, from 35% in RoMa I to 84% in RoMa III (*P*-trend <0.001), and antiarrhythmic medication use rose from 4% to 28% (*P*-trend <0.001).

Risk Assessment and Survival

During a median follow-up of 2115 (interquartile range, 1276–3446) days (~6 years), a total of 83 events occurred. The composite end point included all-cause death (n=3), cardiovascular death (n=10), sudden cardiac death or aborted sudden cardiac death (n=13), heart failure related hospitalization (n=22), stroke or systemic embolism (n=10), surgical myectomy (n=20), and cardiac transplantation (n=5). In total, 68 composite events were recorded, including 13 patients with 2 events and 1 patient with 3 events.

Kaplan–Meier survival estimates (Figure 2) demonstrated significant differences in event-free survival across RoMa groups (log-rank *P*=0.019). Patients in RoMa I had the highest survival, and event rates progressively increased from RoMa II to RoMa IV, reflecting a stepwise gradient in risk.

When pairwise comparisons were performed using log-rank tests, RoMa II, III, and IV each demonstrated significantly worse survival compared with RoMa I (*P*=0.027, 0.006, and 0.002, respectively). Kaplan–Meier curves (Figure 2) clearly illustrate this pattern, with RoMa III and IV showing pronounced divergence from RoMa I after the third year of follow-up. However, differences in log-rank tests across other RoMa groups (eg, II versus III, II versus IV or III versus IV) did not reach statistical significance (Figure S1).

Compared to RoMa I, HRs for the composite end point were 3.16 (95% CI, 1.08–9.28, *P*=0.036) for RoMa II, 4.03 (95% CI, 1.39–11.67, *P*=0.010) for RoMa III, and 4.58 (95% CI, 1.57–13.38, *P*=0.005) for RoMa IV. Other known prognostically relevant variables such as positive genotype, presence or absence of LGE, male sex, reduced LVEF, and LVOT obstruction were not statistically significant in univariable models (Table 2).

Multivariable Cox regression was performed using a model including RoMa and the key clinical covariates: genotype, LVEF <50%, male sex, and LVOT obstruction. LGE was excluded from the multivariable model (>30% missing). Compared to RoMa I, HRs were 3.89 (95% CI, 1.13–13.37, *P*=0.031) for RoMa II, 4.56 (95% CI, 1.32–15.69, *P*=0.016) for RoMa III, and 5.37 (95% CI, 1.54–18.67, *P*=0.008) for RoMa IV. The reference variables, genotype positivity (*P*=0.623), LVEF <50% (*P*=0.914), male sex (*P*=0.155), and LVOT obstruction (*P*=0.510), were not independently associated with the composite outcome.

To further evaluate prognostic performance, we compared models including RoMa, peak VO_2, and VE/VCO_2 slope using identical complete cases (n=291; 68 events; Table 3). Both peak VO_2 and VE/VCO_2 slope alone showed higher discrimination than RoMa (C-index 0.65–0.66 versus 0.60). Adding RoMa to peak VO_2 and VE/VCO_2 slope did not improve model fit ($\Delta df=3$; LR $\chi^2=3.06$; *P*=0.38).

DISCUSSION

In this independent-cohort validation study, we demonstrated that the RoMa classification effectively stratifies patients with HCM into distinct phenotypes and is independently associated with long-term clinical outcomes.

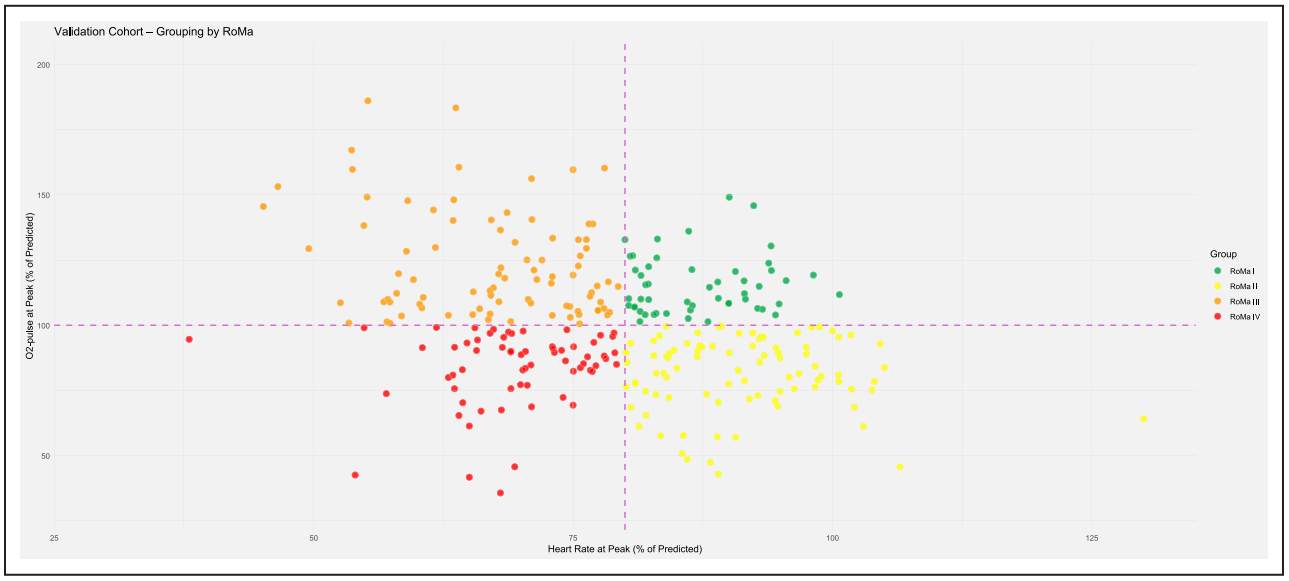

Figure 1. Stratification of patients with HCM according to the RoMa classification.
Distribution of patients with HCM according to the RoMa classification, based on peak HR (% predicted) and peak O_2-pulse (% predicted). Each dot represents an individual patient of the validation cohort, with dashed lines indicating the threshold values used to define group boundaries, as established prior.[10] HCM indicates hypertrophic cardiomyopathy; HR, heart rate; and O_2-pulse, oxygen pulse.

The present cohort exhibited a clear, graded decline in exercise performance across RoMa classes, with peak VO_2, O_2-pulse, and workload declining from RoMa I to IV, paralleled by increasing VE/VCO_2 slopes and diminished VO_2/work relationship slopes. These findings closely mirror those from the original derivation cohort, which was based on a much smaller population (derivation: 90 patients versus validation: 292 patients)[10] and highlight that the classification captures incremental impairment in both circulatory and ventilatory reserve.

Importantly, these changes were partly mirrored by resting echocardiographic features, including typical structural HCM characteristics counting LV wall thickness, LVOT obstruction and prevalence of systolic anterior motion, whereas functional measures of LVEF and prevalence of mitral insufficiency of any degree remained relatively balanced across RoMa categories. This reinforces a key insight: resting structural and functional markers alone might be insufficient to delineate the full spectrum of physiological limitations in HCM. In contrast, exercise-based metrics, particularly those integrated into the RoMa classification, appear to unmask latent impairments in stroke volume reserve, chronotropic response, and pulmonary perfusion that ultimately affect prognosis.[9,20]

In our cohort, RoMa profiles clearly separated patients with preserved versus impaired exercise capacity, with particularly severe impairment in RoMa IV (please see CPET variables in Table 4). Notably, this subgroup (RoMa IV) also had the highest prevalence of systolic anterior motion and higher LV wall thickness, which together contributed to impaired forward flow and offers a connection to the observed functional deterioration from RoMa I to IV. This suggest that exercise underscores pathophysiologic mechanisms that are not clearly detectable at rest, such as dynamic mitral regurgitation or obstructive physiology and emphasizes the need for dynamic evaluation in patient stratification. Integrating CPET and exercise echocardiography in future studies may provide further insights into the mechanisms underlying different RoMa phenotypes. Moreover, devices properly developed to noninvasively assess the cardiac output during exercise (ie, PhysioFlow), may add pathophysiological insights to the main mechanisms related to functional limitations, better defining the single component of the Fick equation.[21]

According to the Fick principle (VO_2=Qc×a–vO_2 difference), both cardiac output and peripheral oxygen extraction contribute to overall oxygen uptake. Because O_2-pulse reflects the product of SV and the a–vO_2 difference, variations in peripheral oxygen extraction may influence the RoMa rationale, particularly in patients with microvascular dysfunction, capillary rarefaction, or mitochondrial inefficiency. Thus, a low O_2-pulse may not exclusively indicate a central limitation in SV reserve but could also reflect impaired peripheral oxygen use. Moreover, the a-vO_2 difference is significantly influenced by exercise-induced blood flow distribution so that in patients with low Qc a greater percentage of blood flow is diverted toward the working muscle counterbalancing the low Qc.[22]

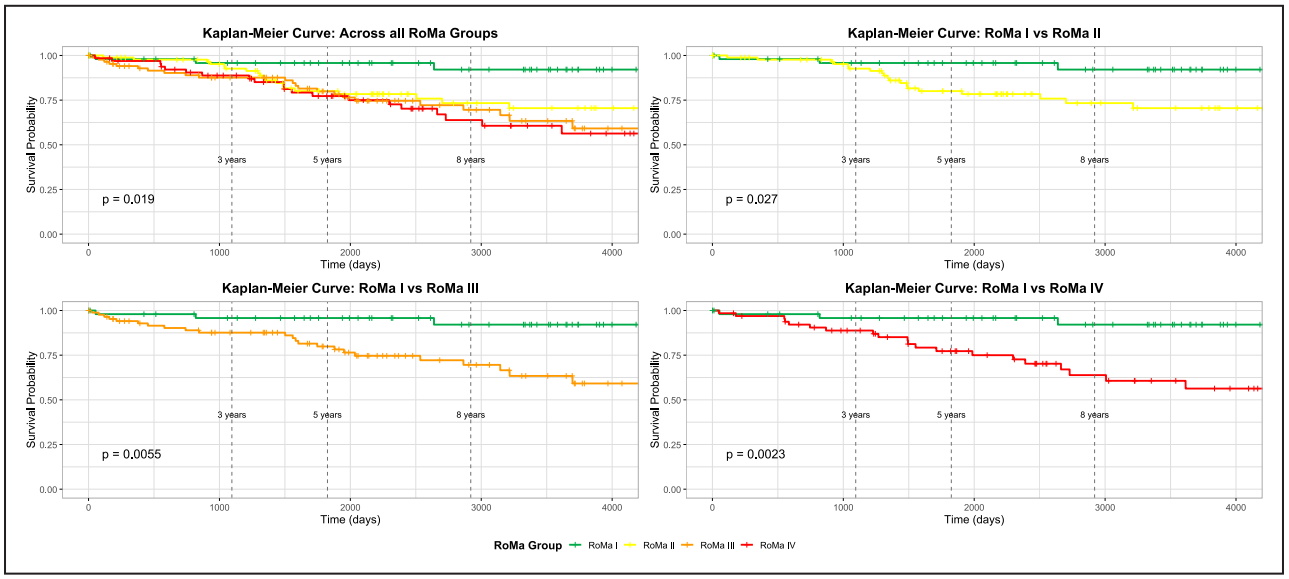

Figure 2. Kaplan–Meier survival curves illustrating event-free survival across RoMa.
Top left, overall survival differences across all 4 RoMa groups (log-rank *P*=0.017), with a clear stepwise decline in survival from RoMa I to RoMa IV. Pairwise comparisons further highlight this gradient: RoMa II vs RoMa I (**top right**, log-rank *P*=0.027), RoMa III vs RoMa I (**bottom left**, log-rank *P*=0.0055), and RoMa IV vs RoMa I (**bottom right**, log-rank *P*=0.0023). Survival probabilities were calculated from the date of cardiopulmonary exercise test to the occurrence of the composite outcome or censoring. Vertical dashed lines indicate 3, 5, and 8 years. CPET indicates cardiopulmonary exercise testing.

Nevertheless, the consistent stepwise decline in VO_2 and O_2-pulse across groups, together with rising VE/VCO_2 slopes, supports the interpretation that central hemodynamic impairment remains the predominant driver of functional limitation within the RoMa framework. Future studies combining CPET with near-infrared spectroscopy or both invasive and noninvasive hemodynamics (ie, with devices capable of estimating SV through bioimpedance measurements, such as PhysioFlow[10]) may further clarify the contribution of peripheral extraction to different RoMa phenotypes. Nonetheless, although a more comprehensive assessment using multiple tools may provide better discrimination of the site of limitation (peripheral versus cardiac), the advantage of the RoMa classification lies in its simplicity and applicability even with a standard CPET using variables that are routinely collected.

Clinical Stratification by RoMa

Kaplan–Meier analyses demonstrated significantly reduced event-free survival in patients with worse RoMa profiles, and this relationship persisted in multivariable models adjusting for established risk markers including genotype, LVEF, male sex, and LVOT obstruction. Compared to RoMa I, HRs for adverse events rose progressively across RoMa II, III, and IV, supporting a dose–response association between reduced functional reserve and clinical outcomes. These associations were stronger than those for traditional prognostic markers (please see HRs for univariable cox regression) such as LGE[13] or genotype positivity,[15] both of which were not predictive in our cohort (although data on LGE were available in only 178 (61%) patients). Nevertheless, our findings highlight the additive prognostic power of exercise-related markers, particularly when structured into a multidimensional classification like RoMa.

To further contextualize these findings, we performed direct model comparisons between RoMa and traditional CPET variables used for prognostication in HCM (peak VO_2 and VE/VCO_2 slope) using identical complete cases (Table 3), where we confirmed that peak VO_2 and VE/VCO_2 slope remain statistically stronger predictors. However, RoMa captures prognostic information through a distinct physiological perspective. Whereas peak VO_2 reflects overall exercise capacity influenced by both cardiac and peripheral factors, RoMa integrates chronotropic reserve and oxygen pulse. Because SV reserve is frequently impaired in HCM due to diastolic dysfunction or dynamic LVOT obstruction, RoMa may more directly reflect the central hemodynamic limitation rather than overall functional performance.[23–25] Thus, RoMa complements rather than replaces traditional CPET variables by providing mechanistic context that can enhance patient phenotyping and potentially the interpretation of interventional strategies, particularly given the growing importance of drugs specifically designed to reduce inotropism without affecting HR (ie, mavacamten and aficamten). A functional evaluation that also includes RoMa may allow to focus attention on the specific components affected by treatment in HCM.

Table 2. Characteristics Across RoMa Groups Within the Validation Cohort

	RoMa I (No.=51)	RoMa II (No.=89)	RoMa III (No.=87)	RoMa IV (No.=65)	*P* trend	*P* value
Demographics						
Male sex, No. (%)	36 (71)	72 (81)	53 (61)	44 (68)	0.148	0.034
Age, y	52 (38–60)	48 (33–62)	57 (43–66)	47 (27–59)	0.810	0.002
Weight, kg	76 (70–82)	74 (68–82)	76 (69–88)	73 (64–89)	0.593	0.490
Height, cm	173±8	172±9	169±10	171±11	0.129	0.095
Body mass index, kg/m^2	24.6 (22.9–27.1)	25.1 (22.8–26.7)	26.8 (23.6–30.1)	25.1 (23.2–28.4)	0.082	0.003
Body surface area m^2	1.9±0.2	1.9±0.2	1.9±0.2	1.9±0.3	0.967	0.839
LV outflow tract obstruction, No. (%)	26 (51)	52 (58)	76 (87)	51 (79)	<0.001	<0.001
Hypertrophic cardiomyopathy genotype positive, No. (%)	28 (55)	54 (61)	39 (45)	34 (52)	0.316	0.165
Cardiopulmonary exercise testing						
Ramp protocol, Watt/min	15 (10–15)	12 (10–15)	10 (8–15)	10 (8–15)	<0.001	<0.001
Systolic blood pressure at rest, mmHg	120 (110–130)	120 (110–130)	120 (110–136)	110 (100–121)	0.089	0.110
Diastolic blood pressure at rest, mmHg	75 (70–80)	70 (70–80)	80 (69–80)	70 (69–80)	0.391	0.332
Heart rate at rest, bpm	72 (63–88)	83 (70–93)	62 (55–68)	69 (61–74)	<0.001	<0.001
VO_2 @ AT, mL/min	1320 (1113–1588)	1130 (894–1346)	1025 (820–1355)	889 (747–1172)	<0.001	<0.001
VO_2 @ AT, mL/kg/min	17.6 (15.5–21.8)	15.3 (12.5–17.6)	13.5 (11.6–15.7)	11.7 (10.2–14.5)	<0.001	<0.001
Heart rate @ AT, bpm	107 (94–121)	110 (101–126)	86 (78–95)	95 (86–101)	<0.001	<0.001
Workload @ AT*, Watt	90 (64–95)	65 (50–89)	60 (41–78)	53 (34–66)	<0.001	<0.001
O_2-pulse @ AT, mL/beat	12.5 (9.7–14.4)	9.9 (8.4–11.8)	12.0 (10.0–14.5)	10.4 (8.0–11.8)	0.222	<0.001
VO_2 @ peak, mL/min	2261 (1846–2707)	1823 (1394–2115)	1699 (1165–2093)	1366 (1082–1841)	<0.001	<0.001
VO_2 @ peak, mL/kg/min	29.2 (25.2–33.7)	24.3 (20.4–28.5)	20.7 (17.0–24.3)	17.9 (14.6–22.8)	<0.001	<0.001
VO_2 @ peak, % predicted	99 (90–107)	77 (66–83)	82 (71–91)	62 (52–67)	<0.001	<0.001
Heart rate @ peak, bpm	149±16	158±19	111±19	123±19	<0.001	<0.001
Heart rate reserve, bpm	74±15	75±18	50±19	55±18	<0.001	<0.001
Systolic blood pressure at peak, mmHg	180 (163–190)	165 (150–180)	160 (140–190)	150 (130–170)	<0.001	<0.001
Diastolic blood pressure at peak, mmHg	90 (81–100)	90 (80–100)	90 (80–100)	80 (80–90)	<0.001	0.003
Workload @ peak, Watt	165 (120–175)	131 (95–157)	115 (77–145)	90 (67–135)	<0.001	<0.001
O_2-pulse @ peak, mL/beat	15.7 (12.1–17.3)	11.8 (8.9–13.3)	15.0 (10.9–17.4)	12.0 (8.6–14.0)	0.035	<0.001
Ventilation to carbon dioxide production slope	25.9 (23.9–28.6)	27.6 (25.1–31.1)	28.0 (24.9–31.9)	28.7 (24.9–33.8)	0.001	0.005
VO_2/work slope, mL/min/W	11.7 (11.0–12.5)	10.6 (9.7–11.5)	10.9 (9.7–12.0)	10.2 (9.4–11.2)	<0.001	<0.001
Respiratory reserve, %	46 (37–51)	48 (38–57)	47 (37–55)	56 (46–63)	<0.001	<0.001
Peak ventilation, L/min	78 (62–89)	70 (54–82)	57 (45–79)	55 (39–69)	<0.001	<0.001
Respiratory quotient @ peak	1.1 (1.0–1.1)	1.1 (1.1–1.2)	1.1 (1.0–1.2)	1.1 (1.0–1.2)	0.247	<0.001
O_2-pulse @ peak, % predicted	112 (107–121)	83 (74–92)	117 (107–135)	88 (77–93)	NA	NA
Heart rate @ peak, % predicted	86 (82–92)	91 (84–97)	68 (60–75)	70 (66–75)	NA	NA

(*Continued*)

Table 2. Continued

	RoMa I (No.=51)	RoMa II (No.=89)	RoMa III (No.=87)	RoMa IV (No.=65)	*P* trend	*P* value
Imaging at rest						
LV diastolic diameter (echocardiography), mm	46±5	46±6	46±6	45±5	0.762	0.858
LV systolic diameter (echocardiography), mm	31 (24–40)	31 (25–40)	29 (24–37)	32 (26–42)	0.753	0.360
Max wall thickness (echocardiography), mm	18 (16–19)	20 (17–22)	20 (16–23)	22 (17–27)	<0.001	<0.001
LV ejection fraction (echocardiography), %	65 (60–65)	62 (60–65)	65 (60–65)	60 (59–65)	0.225	0.062
Mitral insufficiency						
Present at any degree, No. (%)	20 (39)	37 (42)	43 (49)	29 (45)	0.325	0.582
Not present, No. (%)	31 (61)	52 (58)	43 (49)	35 (54)		
Mild, No. (%)	18 (35)	33 (37)	30 (34)	22 (34)		
Moderate, No. (%)	2 (4)	3 (3)	12 (14)	7 (11)		
Severe, No. (%)	0 (0)	1 (1)	1 (1)	0 (0)		
Systolic anterior motion*, No. (%)	4 (8)	13 (15)	29 (33)	12 (18)	0.001	0.004
Late gadolinium enhancement (MRI)*, No. (%)	18 (35)	40 (45)	50 (57)	19 (29)	0.214	0.087
Heart rhythm and device therapy						
Atrial fibrillation, No. (%)	0 (0)	5 (6)	0 (0)	4 (6)	0.338	0.020
Stimulated QRS at presentation, No. (%)	0 (0)	0 (0)	3 (3)	3 (5)	0.021	0.098
Left BBB, No. (%)	0 (0)	2 (3)	5 (6)	2 (3)	0.198	0.428
Right BBB, No. (%)	1 (2)	4 (4)	2 (2)	2 (3)	0.925	0.796
Paced rhythm, No. (%)	2 (4)	7 (8)	9 (10)	2 (3)	0.865	0.436
Pacemaker, No. (%)	0 (0)	1 (1)	4 (5)	3 (5)	0.053	0.232
Implantable defibrillator, No. (%)	0 (0)	7 (8)	5 (6)	13 (20)	<0.001	<0.001
Cardiac resynchronization therapy, No. (%)	0 (0)	0 (0)	0 (0)	1 (2)	0.148	0.364
Pharmacological and surgical therapy						
Previous myectomy, No. (%)	0 (0)	1 (1)	3 (3)	3 (5)	0.060	0.312
Beta-blocker use, No. (%)	18 (35)	48 (54)	73 (84)	46 (71)	0.<0.001	<0.001
Calcium channel blocker, No. (%)	8 (16)	7 (8)	6 (7)	7 (11)	0.460	0.351
Ivabradine, No. (%)	0 (0)	1 (1)	0 (0)	1 (2)	0.540	0.662
Antiarrhythmic medication, No. (%)	2 (4)	2 (2)	16 (18)	18 (28)	0.<0.001	<0.001
Diuretic therapy, No. (%)	4 (8)	13 (15)	13 (15)	13 (20)	0.0.081	0.320
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, No. (%)	16 (31)	26 (29)	29 (33)	21 (32)	0.696	0.940

Summarizes demographics, cardiopulmonary exercise testingperformance, echocardiographic and MRI findings, rhythm and device status, and medical or surgical therapies across the 4 RoMa groups. Continuous variables are presented as mean±SD or median (interquartile range), and categorical variables as counts with percentages. *P* trend values reflect ordered comparisons across RoMa I to IV, and *P* values refer to overall group-wise differences.

AT indicates anaerobic threshold; BBB, bundle-branch block; LV, left ventricular; MRI, magnetic resonance imaging; and VO_2, oxygen uptake.

*>30% but <50% missing.

Table 3. Univariable and Multivariable Cox Proportional Hazards Models for RoMa

Univariable Cox Proportional Hazards Models		
Comparison	**HR (95% CI)**	***P* value**
RoMa II vs RoMa I	3.16 (1.08–9.28)	0.036
RoMa III vs RoMa I	4.03 (1.39–11.67)	0.010
RoMa IV vs RoMa I	4.58 (1.57–13.38)	0.005
RoMa III vs RoMa II	1.25 (0.68–2.27)	0.473
RoMa IV vs RoMa II	1.46 (0.79–2.69)	0.227
RoMa IV vs RoMa III	1.15 (0.64–2.07)	0.648
Positive genotype	1.20 (0.69–2.07)	0.520
Male sex	0.65 (0.40–1.07)	0.089
Late gadolinium enhancement (present vs absent)	0.97 (0.48–1.97)	0.933
LVEF <50%	1.34 (0.42–4.32)	0.622
LVOT obstruction	1.75 (0.97–3.15)	0.063
Multivariable Cox Proportional Hazards Models		
Comparison	**HR (95% CI)**	***P* value**
RoMa II vs RoMa I	3.89 (1.13–13.37)	0.031
RoMa III vs RoMa I	4.56 (1.32–15.69)	0.016
RoMa IV vs RoMa I	5.37 (1.54–18.67)	0.008
Positive genotype	1.15 (0.65–2.04)	0.623
LVEF <50%	1.17 (0.25–4.64)	0.914
Male sex	0.67 (0.38–1.16)	0.155
LVOT obstruction	1.27 (0.63–2.55)	0.510

Univariable analysis (top panel) demonstrates a significant stepwise increase in risk across RoMa groups, with RoMa II, III, and IV all associated with a higher hazard of adverse outcomes compared with RoMa I. Additional comparisons across RoMa subgroups and clinical variables such as genotype status, LVEF <50%, and sex are also reported (68 events, 224 censored). Multivariable analysis (bottom panel), adjusted for genotype, LVEF <50%, and male sex, confirms the independent prognostic value of RoMa classification, with RoMa II, III, and IV all significantly associated with increased risk compared with RoMa I. The model was based on complete cases (59 events, 187 censored), with an events-per-variable ratio of 9.8. HR indicates hazard ratio; LVEF, left ventricular ejection fraction; and LVOT, left ventricular outflow tract.

Regarding clinical outcomes, the lack of a statistically significant difference between RoMa II/III and IV likely reflects overlapping physiological severity rather than a true absence of gradation in risk. Patients in these groups share both a reduction in at least 1 key reserve, either chronotropy or the surrogate for SV, and a similar burden of structural disease and medication use (notably beta blockers). The limited number of events within each subgroup, together with pharmacologic HR suppression and heterogeneous mechanisms of limitation, may have limited the statistical separation between advanced RoMa stages. Despite this, the trend of progressively rising hazard ratios from RoMa I through IV supports a continuous relationship between impaired reserve and outcome risk, consistent with the physiological rationale of the classification. Most important, the RoMa classification, on top of prognosis, was thought to provide the basis of a physiologically guided therapy.

These findings position themselves timely and in a clinically relevant fashion as randomized trials in HCM increasingly incorporate CPET end points to evaluate treatment efficacy.[4–8] Indeed, the need for more nuanced stratification tools is becoming apparent. Traditional single-parameter approaches, such as peak VO_2 alone, may fail to fully reflect the heterogeneous responses to therapy or identify patients most likely to benefit.[26] Indeed, recent trials such as EXPLORER-HCM[8] (Clinical Study to Evaluate Mavacamten [MYK-461] in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy) and SEQUOIA-HCM[6] (Aficamten vs Placebo in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy) have begun integrating composite exercise end points that reflect both peak and submaximal performance. RoMa offers an appealing solution in this context by combining 2 complementary CPET variables into a functional signature of cardiopulmonary reserve, offering a physiologically interpretable measure of disease burden.

It is also noteworthy that our cohort reflects real-world clinical practice, where the majority of patients with HCM are treated with rate-limiting therapies, which may artificially reduce HR reserve due to its pharmacological chronotropic limitation.[27] HR reserve showed a significant declining trend (*P*-trend <0.001) from RoMa I to IV, along with significant reductions in resting HR, HR at the AT, and HR at peak exercise. Despite this, the RoMa classification remained valid and prognostically relevant, as the physiological basis for the classification itself is related to HR response. Although HR response can be attenuated by beta blockers or calcium channel blockers, O_2-pulse, being a potential surrogate for SV during exercise, may provide a therapy-independent marker of physiological reserve, as it might be less influenced by chronotropy mediating medications.[28] This balance of therapy-sensitive and therapy-insensitive parameters (HR and O_2-pulse respectively) might lend RoMa additional robustness in longitudinal monitoring or therapeutic response assessment, however still needing confirmation. Future studies may explore its responsiveness to disease-specific therapy, such as myosin inhibitors, and its potential to guide personalized treatment strategies.

The RoMa classification can be implemented without additional equipment or procedural burden, using standard CPET protocols and widely available reference equations. This makes it scalable and applicable across centers with CPET capability. Given the predictive value demonstrated in this study, incorporating RoMa into existing HCM risk models or disease management pathways may help clinicians better identify high-risk patients and tailor follow-up or therapy accordingly.

Table 4. Prognostic Performance and Incremental Value of RoMa, peak VO_2, and VE/VCO_2 Slope in the Same Cohort

Parameter	C-index	AIC	HR (95% CI)	*P* value
RoMa overall	0.577	691.8	…	…
RoMa II vs I			2.17 (0.72–6.49)	0.167
RoMa III vs I			2.44 (0.81–7.36)	0.112
RoMa IV vs I			2.25 (0.72–7.03)	0.163
Peak VO_2 (per 1 SD ↑)	0.654	675.3	0.68 (0.48–0.96)	0.029
VE/VCO_2 slope (per 1 SD ↑)	0.665	679.7	1.28 (1.01–1.61)	0.037
Peak VO_2+VE/VCO_2 slope	0.662	673.2	…	…
RoMa+VO_2+VE/VCO_2 slope	0.656	676.2	…	…
Model comparison by likelihood-ratio testing				
Model comparison	*Δdf*	*LR* χ^2	…	*P value*
Peak VO_2+VE/VCO_2→peak VO_2+VE/VCO_2+RoMa	3	3.06	…	0.38

Discriminative performance and model fit of the RoMa classification compared with CPET variables in identical complete cases (n=291; 68 events). The C-index (optimism-corrected via bootstrap internal validation, B=200) and AIC are reported for each of the 5 models separately. The HRs were derived from the full combined model (RoMa+Peak VO_2+VE/VCO_2 slope) and represent risk per 1 SD increase in continuous predictors. A nested model comparison was performed using LR testing to evaluate the incremental prognostic value of adding RoMa to the CPET model (peak VO_2+VE/VCO_2 slope). Adding RoMa to the CPET model did not add prognostic value (P=0.38). Statistical significance was reached if p<0.05.

AIC indicates Akaike information criterion; CPET, cardiopulmonary exercise testing; HR, hazard ratio; LR, likelihood ratio; VE/VCO_2, ventilation to carbon dioxide production slope; and VO_2, oxygen uptake.

Limitations

First, this was a retrospective study, which may introduce selection and information biases, particularly in outcome adjudication and follow-up completeness. Although data were drawn from institutional records, event misclassification cannot be entirely excluded. Second, atrial fibrillation, a known adverse prognostic marker in HCM,[29] was present in only a small subset (3%) of the cohort and was therefore not feasible to include in the multivariable analysis due to insufficient statistical power and violating the proportional hazards assumption. Third, LGE data were incomplete (>30% missing) and thus excluded from multivariable models. Of note, we were able to assess LGE only as present or absent. Accordingly, we lost the ability to perform a quantitative and qualitative analysis, which greatly limits the potential of LGE to predict arrhythmic burden in our cohort. Finally, the observational design precludes causal inference or assessment of treatment response. Prospective and interventional studies are needed to establish whether RoMa can guide therapy or monitor clinical improvement. Finally, as this was a retrospective analysis, prospective studies are warranted to confirm these findings and to establish whether the RoMa classification can guide therapy or improve clinical outcomes in patients with HCM.

Conclusions

In summary, this study validates the RoMa classification as a robust, physiologically sound, and prognostically informative tool in HCM regardless of LVOT obstruction. Further external validations and interventional studies will be essential to establish RoMa's utility in guiding therapy and long-term management strategies.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Figure S1
STROBE checklist

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