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Clinical and echocardiographic correlates of acute heart failure, cardiogenic shock and in-hospital mortality in tako-tsubo cardiomyopathy: insights from the "Tako-tsubo Italian Network"

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ABSTRACT

Objective: To determine clinical and echocardiographic correlates of acute heart failure, cardiogenic shock and in-hospital mortality in a large cohort of tako-tsubo cardiomyopathy (TTC) patients.

Background: Despite good long-term prognosis, life-threatening complications due to hemodynamic instability can occur early in TTC patients.

Methods: The study population consisted of 227 patients (66.2 ± 12.2 years; female 90.3%) enrolled in the Tako-tsubo Italian Network, undergoing transthoracic two-dimensional echocardiography on admission and at short-term follow-up [4.3 (4-6) weeks]. Patients were divided into two groups according to the presence or absence of major adverse events, a composite of acute heart failure, cardiogenic shock, and in-hospital mortality.

Results: Major adverse events occurred in 59 patients (25.9%). Elderly patients aged ≥75 years (42.4 vs 23.8%; p=0.011), left ventricular (LV) ejection fraction (35.1 ± 5.9 vs 38.4 ± 4.6%; p<0.001), wall motion score index (1.9 ± 0.2 vs 1.7 ± 0.2; p<0.001), E/e' ratio (13.5 ± 4.3 vs 9.9 ± 3.3; p<0.001), LV outflow tract obstruction (23.7 vs 8.9%, p=0.006), pulmonary artery systolic pressure (47.4 ± 12.3 vs 38.0 ± 9.2 mmHg; p<0.001), right ventricular involvement (28.8 vs 9.5%;p<0.001), and reversible moderate to severe mitral regurgitation (49.1 vs 11.9%; p<0.001) were significantly different between groups and were associated with adverse events. At multivariate analysis, LV ejection fraction (HR 0.92; 95%CI: 0.89-0.95; p<0.001), E/e' ratio (HR 1.13; 95%CI: 1.02-1.24; p=0.011), reversible moderate to severe mitral regurgitation (HR 3.25; 95%CI: 1.16-9.10; p=0.025), and age ≥75 years (HR 2.81; 95%CI: 1.05-7.52; p=0.039) were independent correlates of major adverse events.

Conclusions: Echocardiographic parameters provide additional information compared to other variables routinely used in clinical practice in identifying patients at higher risk of

hemodynamic deterioration and poor in-hospital outcome, allowing prompt institution of appropriate pharmacological treatment and adequate mechanical support.

CONDENSED ABSTRACT

The aim of this study was to determine clinical and echocardiographic correlates of major adverse events, a composite of acute heart failure, cardiogenic shock, and in-hospital mortality, in 227 patients (66.2 ± 12.2 years; female 90.3%) with tako-tsubo cardiomyopathy (TTC) enrolled in the Tako-tsubo Italian Network. At multivariate analysis, left ventricular ejection fraction, E/e' ratio, reversible moderate to severe mitral regurgitation and age ≥75 years were independent correlates of major adverse events that occurred in 59 patients (25.9%). Echocardiographic parameters provide a major contribution to the early identification of TTC patients at higher risk of hemodynamic instability requiring appropriate management.

ABBREVIATIONS

BNP = brain natriuretic peptide

CMR = cardiac magnetic resonance

EF = ejection fraction

LA = left atrial

LV = left ventricular

LVOTO = left ventricular outflow tract obstruction

MR = mitral regurgitation

sPAP = pulmonary artery systolic pressure

RV = right ventricular

TAPSE = tricuspid annular plane systolic excursion

TTC = tako-tsubo cardiomyopathy

WMSI = wall motion score index

INTRODUCTION

Tako-tsubo cardiomyopathy (TTC) is typically characterized by transient left ventricular (LV) systolic dysfunction with morphological features of "apical ballooning", although other variant forms (e.g., midventricular ballooning) have also been described (1-3). It most often occurs in postmenopausal women and is usually triggered by emotional or physical stress, with complete recovery of LV systolic function within a few days or weeks (4,5). Despite its favorable long-term prognosis and very low mortality, TTC is not considered a "benign" condition because of the occurrence of life-threatening complications during the acute phase related to hemodynamic instability (e.g., acute heart failure, cardiogenic shock) in a substantial proportion of patients (6-8). Owing to its widespread use in critical care settings, echocardiography has become the noninvasive imaging modality of choice for assessing TTC (2,9). However, the combination of clinical, electrocardiographic, laboratory and echocardiographic measures routinely used in clinical practice in TTC patients experiencing major adverse events due to hemodynamic instability have not yet been well described. The aim of this study was to identify the clinical and echocardiographic determinants of major adverse events, a composite of acute heart failure, cardiogenic shock and inhospital mortality, in a large cohort of TTC patients.

METHODS

Study population

The study population consisted of 227 patients enrolled in the Tako-tsubo Italian Network (TIN) undergoing comprehensive transthoracic two-dimensional echocardiography on admission and at short-term follow-up [4.3 (4-6) weeks] (8,10). The diagnosis of TTC was based on the Mayo Clinic criteria (5):

• transient akinesia or dyskinesia of LV apical and/or midventricular segments;

• no angiographic evidence of ≥50% coronary artery stenosis, or plaque rupture, or intracoronary thrombus formation;

• new ECG abnormalities (dynamic ST-T changes or T-wave inversion);

• absence of intracranial bleeding, pheochromocytoma, and myocarditis.

Patients with poor acoustic window (suboptimal visualization of endocardial borders) were excluded. All participants provided informed written consent and the study was approved by the local ethics committee.

Data collection

Clinical variables were recorded on a standardized form that included information on patient demographics (sex, age, heart rate, systolic and diastolic blood pressure), signs and symptoms at presentation, medical history, trigger events, ECG ST-segment changes and presence of prolonged QTc interval on admission, and clinical observations during hospitalization (including major cardiac events). Emotional or physical triggers were identified as previously described (8). Venous blood was collected every 3 hours to measure troponin I concentration in the acute phase, and this continued until a peak value was observed. All patients underwent coronary angiography and left ventriculography within 24 hours of symptom onset.

Definition of major adverse events due to hemodynamic instability

Major adverse events were defined as a composite of acute heart failure, cardiogenic shock and inhospital mortality. In particular: - acute heart failure was defined as the presence of pulmonary edema, dyspnea, and/or oxygen desaturation requiring drug therapy and/or mechanical support; - cardiogenic shock was defined as systolic blood pressure <90 mmHg with signs of tissue hypoperfusion requiring inotropic agents and/or fluid therapy; - in-hospital mortality was defined as cardiac death or death from any cause.

Echocardiography

All echocardiographic examinations were performed within 6 hours of hospital admission before coronary angiography, and were repeated 5 ± 1.6 (range 4-6) weeks after symptom onset. A commercially available cardiac ultrasonography system with a 2.5-4.5 MHz phased-array transducer with second harmonic capability was used for complete two-dimensional Doppler echocardiography. All exams were performed by observers blinded to clinical data. LV regional wall motion abnormalities and presence of typical "circular" systolic dysfunction with involvement of ≥4 coronary territories were evaluated by visual assessment of multiple apical and short-axis views, as previously described (9). All echocardiographic images were digitally recorded and reviewed by two expert readers (R.C. and F.R). Three cardiac cycles from the apical 4- and 2- chamber view and the parasternal short-axis view at the level of the mitral valve and papillary muscles were stored in cine-loop format for off-line analysis. LV ejection fraction (EF) was calculated using biplane Simpson's rule from the apical 4- and 2-chamber views (11). Left atrial (LA) volume was assessed by the biplane area-length method and indexed to body surface area (11). Right ventricular (RV) wall motion was evaluated by visual assessment for the detection of RV involvement (12). The echo transducer was adjusted to the level of the RV chamber to achieve optimal visualization of RV size and RV endocardial borders. Tricuspid annular plane systolic excursion (TAPSE) was calculated as previously

described (13). LV diastolic function was evaluated according to the American Society of Echocardiography recommendations (14). Early (e') diastolic tissue Doppler velocities were measured at the septal and lateral corners of the mitral annulus, and the mean between the two values was calculated. The ratio of mitral E peak velocity and averaged e' velocity (E/e') was calculated. Mitral regurgitation (MR) was quantified from color Doppler imaging and semiquantitatively graded as absent, minimal (within normal limits), mild, moderate, or severe using standardized criteria (15). Moderate MR was confirmed by vena contracta measurement (3-7 mm) (16). Reversible significant MR was defined as reversible moderate to severe MR detected during the first echocardiographic evaluation that disappeared at follow-up examination. LV outflow tract obstruction (LVOTO) was detected by continuous wave Doppler. Using the modified Bernoulli equation, a cut-off value of 25 mmHg for dynamic intraventricular pressure gradient was considered to indicate significant LVOTO (17). With continuous-wave Doppler echocardiography, peak tricuspid regurgitant velocity recorded from any view was used to determine pulmonary artery systolic pressure (sPAP) with the simplified Bernoulli equation [sPAP=4(peak velocity)2+mean right atrial pressure]; mean right atrial pressure was estimated as previously described [18].

Statistical analysis

The statistical analyses included descriptive statistics (frequency and percentage of categorical variables, mean and standard deviation of continuous normally distributed variables, and median values and an interquartile range of continuous non-normally distributed variables). The normal distribution of continuous variables was verified with the Kolmogorov-Smirnov goodness-of-fit test. Continuous variables were then compared with independent sample Student's t-test or Mann-Whitney U-test, and categorical variables were compared with chi-square statistic or Fisher's exact test, when appropriate. The associations of selected variables with major adverse events were assessed with Cox

proportional hazard models using univariate and stepwise multivariate procedures. A significance of .05 was required for a variable to be included into the multivariate model, whereas .1 was the cutoff value for exclusion. Hazard ratios (HR) with 95% CIs were estimated. The following covariates were analyzed: age $\geq$ 75, heart rate, chest pain with dyspnea, brain natriuretic peptide (BNP), LVEF, E/e' ratio, sPAP, moderate to severe MR, RV involvement and LVOTO. The Hosmer-Lemeshow statistic was used to assess the goodness-of-fit of the logistic regression model. A p value <0.05 was considered statistically significant. In addition, to investigate the incremental prognostic value of echocardiographic correlates of major adverse events compared with clinical, electrocardiographic and laboratory findings an interactive stepwise procedure was conducted. Therefore, clinical data (including age, sex, presenting symptoms, blood pressure, heart rate) were first analyzed and the global χ2 was calculated. Subsequent steps were created after adding ECG changes at admission, laboratory findings (Troponin I, CK-MB and BNP peak) and independent echocardiographic correlates of major adverse events (moderate to severe MR, E/e' ratio and EF). The incremental prognostic value of the added variables was determined by comparison of the global χ2 calculated at each step. The χ2 of the model was calculated from the log likelihood ratio. A statistically significant increase in global χ2 after the addition of further variables was considered to indicate incremental prognostic value. Statistical analysis was performed using SPSS 20.0 statistical package (SPSS Inc., Chicago, Illinois).

RESULTS

Demographic and clinical characteristics

The study population included 227 patients (66.2 ± 12.2 years; female 90.3%). Demographic, clinical and ECG characteristics of the overall population are shown in Table 1. Patients with and without major adverse events were compared. There was a striking prevalence of females (91.5 vs 89.9%; p=0.80) in menopause (85.1 vs 88.7%; p=0.47) in both groups. A significantly higher proportion of elderly patients aged ≥75 years (42.4 vs 23.8%; p=0.011) was observed among those with major adverse events. Chest pain with dyspnea (25.4 vs 8.9%; p=0.003) and increased heart rate (88.8 ± 20.5 vs 83.4 ± 14.1 bpm; p=0.031) were significantly more frequent among patients with major adverse events. No significant differences were found between groups in ECG presentation, LV morphology, prevalence of triggers, and common cardiovascular risk factors. Conversely, the involvement of ≥4 coronary territories was more frequent (89%) and prevalent in patients with hemodynamic instability [57 (96.6%) vs 147 (87.5%) patients; p=0.047]. Length of hospital stay was significantly longer in patients with major adverse events [9 (5-12.2) vs 6 (5-9) days; p=0.002].

Major adverse events (acute heart failure, cardiogenic shock and in-hospital mortality)

Overall complications are listed in Table 2. Acute heart failure was the most common major complication (n=45; 19.6%). Among patients with acute heart failure, 5 patients had cardiogenic shock, 1 patient had cardiogenic shock and stroke, 3 patients had ventricular tachycardia/fibrillation, 1 patient had ventricular tachycardia/fibrillation and atrial fibrillation, 2 patients had atrial fibrillation alone, and 1 patient had apical thrombosis. Among patients with cardiogenic shock (n=18; 7.8%), 3 had active cancer, 1 had stroke and preexisting atrial fibrillation, and another one had new-onset atrial fibrillation. Thirteen (5.7%) patients with cardiogenic shock were treated with positive inotropic drugs

or vasopressors or both (dobutamine at an infusion rate of 2-20 μg/kg/min; norepinephrine at an infusion rate of 0.2-1.0 μg/kg/min, or levosimendan at an infusion rate of 0.1 μg/kg/min). Despite treatment, 3 patients died during intensive care unit stay. Intra-aortic balloon pumping was used in 6/18 patients with cardiogenic shock admitted to facilities where implantation of the device could be performed. Of note, 10 patients with cardiogenic shock had reversible moderate to severe MR. Death occurred in 6 patients (2.6%). Cardiac death was related to cardiogenic shock in 3 patients and to acute heart failure in 1 patient. Non-cardiac death was associated with malignancy in the remaining 2 patients. Among 11 patients with ventricular tachycardia/fibrillation, only 1 had torsade de pointes and 9 had prolonged QTc intervals (p=0.012).

Echocardiographic findings on admission (Table 3)

Patients with major adverse events had significantly higher indexed LV end-diastolic volume (p=0.002) and LV end-systolic volume (p<0.001), lower EF (p<0.001), higher wall motion score

index (WMSI) (p<0.001) and larger LA volume (p<0.001) than patients without major adverse events. Regarding diastolic function, all mitral inflow-derived parameters were significantly different between groups: E peak velocity (p<0.001), E/A ratio (p<0.001), E-wave deceleration time (p=0.011), e' peak velocity (p=0.007) and E/e' ratio (p<0.001; figure 1). In the overall population, LVOTO was detected in 29 patients (only 2 received inotropic agents) and was more common in patients with major adverse events (p =0.006). Reversible moderate to severe MR was detected in 49 patients and was prevalent in patients with major adverse events (49.1 vs 11.9%, p<0.001; figure 2). Acute heart failure and cardiogenic shock occurred in 28/49 patients (57%). Patients with moderate to severe MR had lower EF [median (IQ) = 38% (31-40) vs 40% (36-42)] than patients without significant MR. Apical ballooning (40/49 patients; 81%) was prevalent in this subgroup.

Seventeen patients had concomitant LVOTO and systolic anterior motion (34.6%). RV involvement (28.8 vs 9.5%; p=0.001) was more frequent among patients with major adverse events. Indexes of LV filling pressure, such as E/e' ratio (p<0.001) and sPAP (p<0.001), were significantly higher, suggesting a more compromised hemodynamic status in the group with major adverse events.

Echocardiographic findings at short-term follow-up (Table 4)

At short-term follow-up, all echocardiographic measures examined were not significantly different between groups, except for LA volume (p<0.001), E peak velocity (p=0.002), E/A ratio (p=0.001), e' peak velocity (p<0.001), E/e' ratio (p<0.001), and sPAP (p=0.027) that remained higher in patients who experienced major adverse events.

Independent clinical and at admission echocardiographic correlates of major adverse events (Table 5).

At univariate analysis, age ≥75 years, heart rate, LVOTO, RV involvement, chest pain with dyspnea, LVEF, E/e' ratio, sPAP, and presence of moderate to severe MR at admission were significantly associated with the occurrence of major adverse events. At multivariate analysis, LVEF, E/e' ratio, reversible moderate to severe MR and age ≥75 years were independent correlates of the composite outcome (Table 5). When considering only two of the three components of the composite outcome, i.e. cardiogenic shock and death, heart rate (HR 1.028, 95%CI 1.004-1.052, p=0.022), LVEF (HR 0.872, 95%CI 0.819-0.928, p<0.001) and reversible moderate to severe MR (HR 4.498, 95%CI 1.366-14.811, p=0.013) were identified as independent predictors. The Hosmer-Lemeshow statistic was not significant (p=0.45), indicating a good model fit.

Incremental prognostic value of independent echocardiographic correlates of major adverse events.

Sequential models for the prediction of major adverse events were used to assess the incremental contribution of echocardiographic correlates of major adverse events

compared with clinical, electrocardiographic and laboratory findings. For major adverse events, the clinical model ($\chi 2$ 40.7, p < 0.001) was slightly but not significantly improved by the addition of electrocardiographic ($\chi 2$ 46.2, p = 0.24) and laboratory data ($\chi 2$ 50.9, p = 0.19) respectively. A major and significant improvement was obtained only by the addition of echocardiographic findings ($\chi 2$ 88.7, p < 0.001; figure 3).

DISCUSSION

This study addresses the role of echocardiography compared with other clinical, electrocardiographic and laboratory measures routinely used in daily practice in the early evaluation of patients with TTC. The main findings can be summarized as follows: 1) in a large series of TTC patients, approximately 25% developed pulmonary edema or cardiogenic shock during the acute phase; 2) several echocardiographic findings, such as LVEF, WMSI, E/e' ratio, LVOTO, sPAP, RV involvement and reversible moderate to severe MR, are associated with such adverse events; 3) LVEF, reversible moderate to severe MR, E/e' ratio, and age ≥75 years are independent correlates of acute heart failure, cardiogenic shock and in-hospital mortality. In addition, the prevalence of some peculiar echocardiographic findings previously reported in small cohorts of TTC patients have been documented in a larger series.

Clinical relevance of systolic and diastolic echocardiographic parameters

The majority of patients with TTC are usually paucisymptomatic and have a favorable in-hospital course. However, adverse events due to hemodynamic instability (e.g., acute heart failure, or cardiogenic shock) may occur in up to one quarter of patients even during the first hours after clinical onset.

In our study, higher WMSI and lower LVEF were associated with pulmonary edema and cardiogenic shock, confirming that marked LV systolic dysfunction contributes to the development of hemodynamic instability (7). Increased sympathetic stimulation seems to play a central role in the occurrence of systolic impairment related to myocardial stunning in TTC patients through a variety of pathophysiological mechanisms, including myocyte calcium overload, oxidative stress and microvascular dysfunction (4,19,20). Lower peak levels of cardiac enzymes are observed in TTC compared with acute coronary syndrome, despite more pronounced myocardial dysfunction. The slight elevation of troponin and CK seems to be associated with myocardial stunning rather than necrosis, as abnormal

troponin levels do not necessarily indicate true myocardial damage. The potential role of ECG abnormalities in predicting adverse events in TTC has been previously investigated (21). In the study of Takashio et al. the magnitude and extent of ST-segment elevation on the ECG were found to be independent predictors of in-hospital adverse events (21). However, these findings were not confirmed by other authors (22). Although ST-segment elevation is the most common ECG presentation, it is detected in roughly 50% of patients, especially in Western countries (23). In clinical practice, a marked disproportion between troponin peak levels and the magnitude of ECG changes compared with the extent of regional myocardial dysfunction is frequently observed. Our results demonstrate that LVEF is an independent correlate of acute heart failure and is superior to troponin and ECG in identifying patients at risk of hemodynamic instability. Echocardiography seems to better mirror the amount of dysfunctioning myocardium than ECG alterations and serum parameters, confirming the importance of multiparametric LV assessment in TTC patients. TTC patients may show volume and pressure overload secondary not only to acute systolic but also diastolic dysfunction. Interestingly, advanced age and female gender that typically prevail in TTC were found to be associated with LV diastolic stiffening coupled with a stiff vascular system and endothelial dysfunction (24). Basal hyperkinesis and apical LV wall stress induce intraventricular diastolic and systolic pressure gradients and are believed to be the primary mechanisms responsible for increased LV filling pressure in this peculiar cardiomyopathy. In TTC patients, elevated B-type natriuretic peptide (BNP) levels were shown to correlate with the severity of LV diastolic dysfunction independent of troponin peak levels (25). In our study as well as in other series, E/e' ratio was elevated (26). A relationship between decreased LV untwisting (a regional diastolic index) and increased E/e' ratio (a global diastolic index) has been reported, demonstrating that diastolic function is impaired even in the early phase of TTC (27). E/e' ratio is considered a good predictor of LV filling pressure and it has already been proven useful in predicting outcome in

different cardiovascular diseases, also showing an incremental prognostic value as compared to BNP (28). Our study demonstrates for the first time that E/e' ratio is a strong determinant of acute heart failure and in-hospital mortality in patients with TTC. This parameter should therefore be assessed early and systematically in order to identify patients at higher risk of hemodynamic instability and to guide appropriate management. In addition, the improvement in E/e' ratio and LV systolic function at follow-up may be considered a useful indicator of LV function recovery (Figure 1). Heart failure can also be precipitated by elevated pulmonary artery pressure usually related to reduced LA compliance (advanced LV diastolic dysfunction in elderly patients) or LA volume overload (significant MR) (28). Of note, in our study, the echocardiographic parameters of both systolic and diastolic function, including E/e' ratio, were significantly more compromised in patients with adverse events than in those without. At short-term assessment, despite comparable recovery of systolic function, some parameters of diastolic function (namely, E/A ratio, E/e' ratio, and LA volume) remained significantly out of the normal range in patients who experienced adverse events. As a possible explanation for this finding, it may be hypothesized that preexisting diastolic dysfunction may have been unmasked following the resolution of the acute phase, suggesting that TTC patients with impaired diastolic function are more prone to develop acute heart failure.

Reversible mitral regurgitation, acute heart failure and cardiogenic shock

Several aspects regarding the impact of reversible significant MR on the clinical picture of TTC patients are still debated. First, the true incidence remains to be clearly defined. In our study population, reversible significant (moderate to severe) MR during the acute phase was observed in 21% of TTC patients. This finding is consistent with the prevalence (range 19-25%) reported in the literature (29-31). Second, also etiology of acute MR remains to be fully elucidated. Two distinct underlying mechanisms seem to be associated with the development of MR in TTC: 1) the coexistence of systolic anterior motion and LVOTO,

and 2) tethering of the mitral valve leaflets (31). In our study, only a minority of patients with significant MR showed concomitant LVOTO and systolic anterior motion (7%), confirming the hypothesis that different underlying mechanisms may induce dynamic functional MR. Finally, not univocal data on the association of MR with ballooning pattern, systolic function and prognosis have been reported so far. In our study, patients with significant MR had a striking prevalence of apical ballooning pattern and, if compared with patients without MR, had a lower EF. These findings lead us to hypothesize that significant MR may be associated with more extensive myocardial dysfunction. It is unquestionable that in a context of stunning myocardium, typical of TTC, the left ventricle can compensate for the development of an acute MR by increasing preload and emptying, as expected in a normal ventricle [32]. LV volume overload results in increased myocardial tension that, in a vicious circle, leads to systolic dysfunction and reduced stroke volume [33]. Ejection of the regurgitant volume into the left atrium before aortic valve opening further reduces forward effective cardiac output predisposing to cardiogenic shock. In addition, LA pressure rises abruptly, especially in the presence of normal or reduced LA compliance, often leading to pulmonary congestion and acute heart failure. In our study, 18 patients developed cardiogenic shock and among these 10 (55%) had moderate to severe MR. The prevalence of cardiogenic shock in TTC was 15% in the study of Tsuchihashi et al., but even rarer in other series [1,34]. Song et al. reported the occurrence of cardiogenic shock in 16 of 50 (32%) TTC patients [35]. Patients with cardiogenic shock had a significantly higher prevalence of reversible MR and apical ballooning pattern than patients without cardiogenic shock. Our data are consistent with those of Song et al. demonstrating that reversible moderate to severe MR is an independent determinant of major adverse events [35]. In addition, reversible MR remained a significant independent correlate even after considering cardiogenic shock and death as the only components of the composite outcome. Owing to its potential negative impact on in-hospital course, early

echocardiographic assessment of the mitral valve should be performed, with special attention to hemodynamics in moderate to severe MR, in particular in patients with advanced systolic dysfunction and LVOTO. LVOTO has been reported in 25% of patients in a small series of 32 TTC patients (17). In our larger population, the prevalence of LVOTO was 12.8%. LVOTO should be systematically ruled out by echocardiography in order to implement an appropriate therapeutic strategy. In patients with LVOTO and markedly impaired LV systolic function, ß-blockade and intra-aortic balloon counterpulsation should be the preferred treatment options when compared to inotropic agents to prevent the development of significant intraventricular gradients and subsequent hemodynamic deterioration (36).

STUDY LIMITATIONS

Several issues should be considered when interpreting these data. First, only patients with good acoustic windows were evaluated. Although our intraobserver and interobserver variability in evaluating LV wall motion contraction was good (9), visual assessment of wall motion may have been affected by the tethering phenomenon. Second, catecholamine levels were not reported. However, our observation reflects clinical practice in a real-world setting, where measurement of catecholamine levels is not systematically performed in the acute phase of TTC. In addition, up to date the link between sympathetic activation, elevated circulating catecholamines and the occurrence of stunned myocardium in TTC remains hypothetical [37]. It would have been of interest to compare the association of echocardiographic and cardiac magnetic resonance (CMR) parameters in TTC patients with and without complications. In a prospective study, Eitel et al. reported robust data on cardiac CMR in a large cohort of TTC patients enrolled from 7 tertiary care centers in Europe and North America [38]. However, their series included only one patient with cardiogenic shock, probably because CMR is difficult to perform in patients with hemodynamic instability. Finally, cardiac CMR is not largely available and not systematically used, especially in the early evaluation of patients with acute coronary syndrome or similar conditions.

CONCLUSIONS

Echocardiographic parameters provide additional information compared to other variables routinely used in clinical practice in identifying patients at higher risk of hemodynamic deterioration and poor in-hospital outcome. Our study demonstrates for the first time that LVEF, reversible moderate to severe MR, E/e' ratio, and age ≥75 years are independent correlates of major adverse events (i.e., acute heart failure, cardiogenic shock and in-hospital mortality) in a large cohort of TTC patients. Comprehensive seriated echocardiographic examinations should be systematically performed in patients with TTC to monitor systolic and diastolic LV function recovery. Special attention should be paid to patients with significant MR and intraventricular obstruction to promptly institute appropriate pharmacological treatment and adequate mechanical support.

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FIGURES

Figure 1: Pulsed-wave (PW) of mitral inflow (upper panels) and PW tissue Doppler of the mitral annulus (lower panels) at admission (left) and recovery (right) in patient with apical TTC complicated by acute heart failure. Note the high E/e' ratio in the acute phase that markedly reduce at the time of recovery. A, late LV filling; a', late myocardial velocity; E, early LV filling; e', protodiastolic myocardial velocity; s, systolic myocardial velocity.
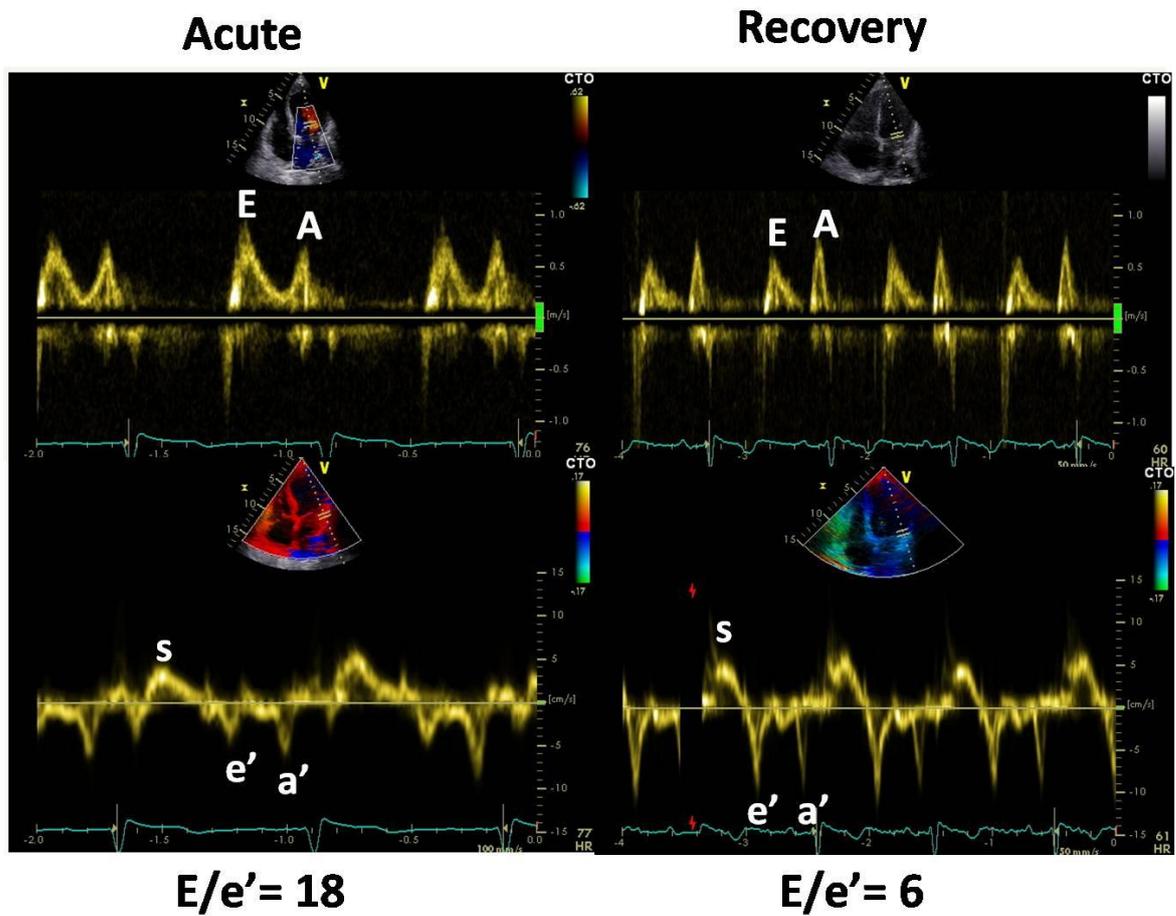
Figure 2: In the upper panel moderate MR in TTC patient with chest pain and heart failure at admission. In the same patient a reduction of MR at discharge can be appreciated (lower panel). LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.
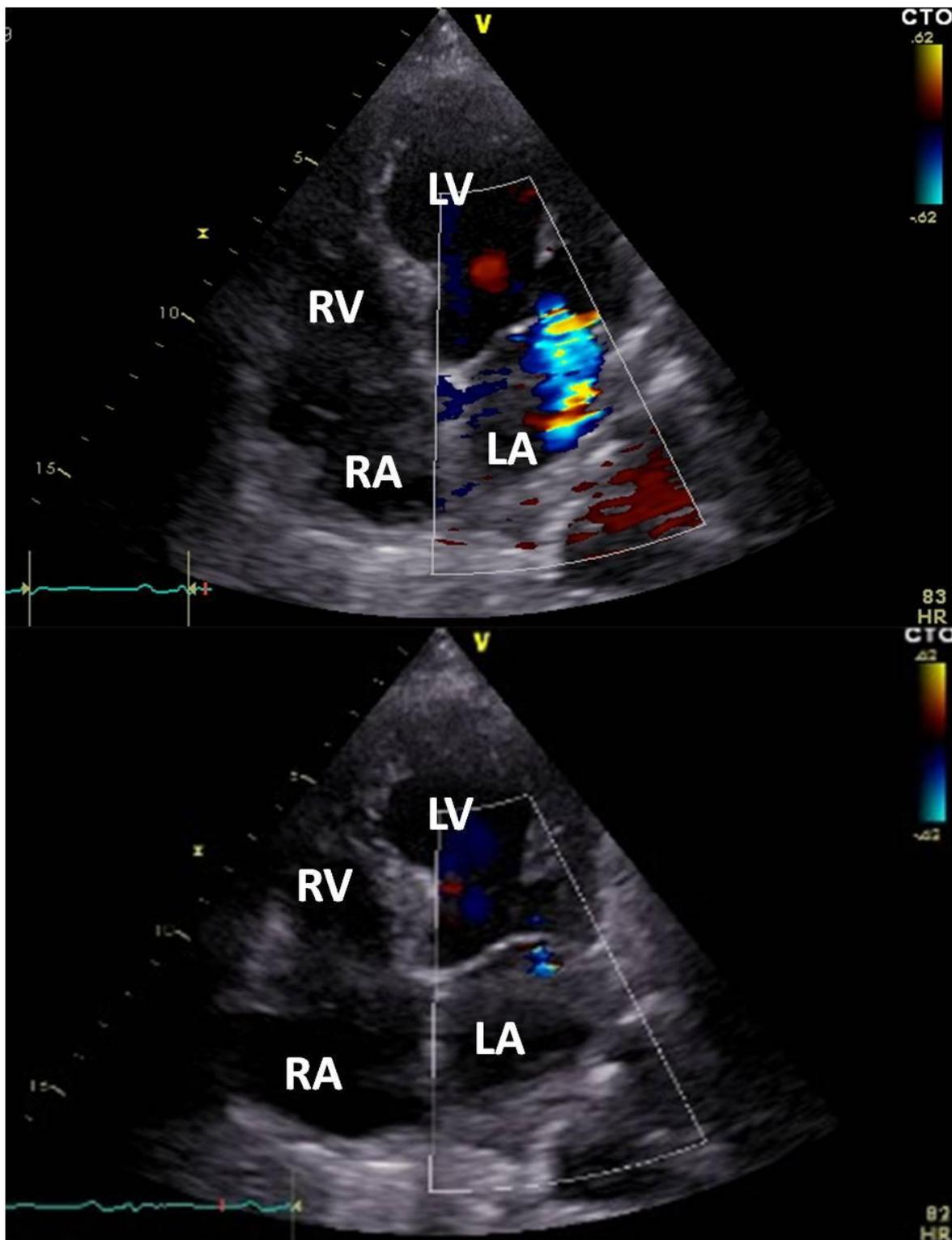
Figure 3: Incremental prognostic value of independent echocardiographic correlates (Echo) of major adverse events to clinical data, elctrocardiographic (ECG) changes at admission, laboratory findings as determined by the comparison of the global χ2 at each step.
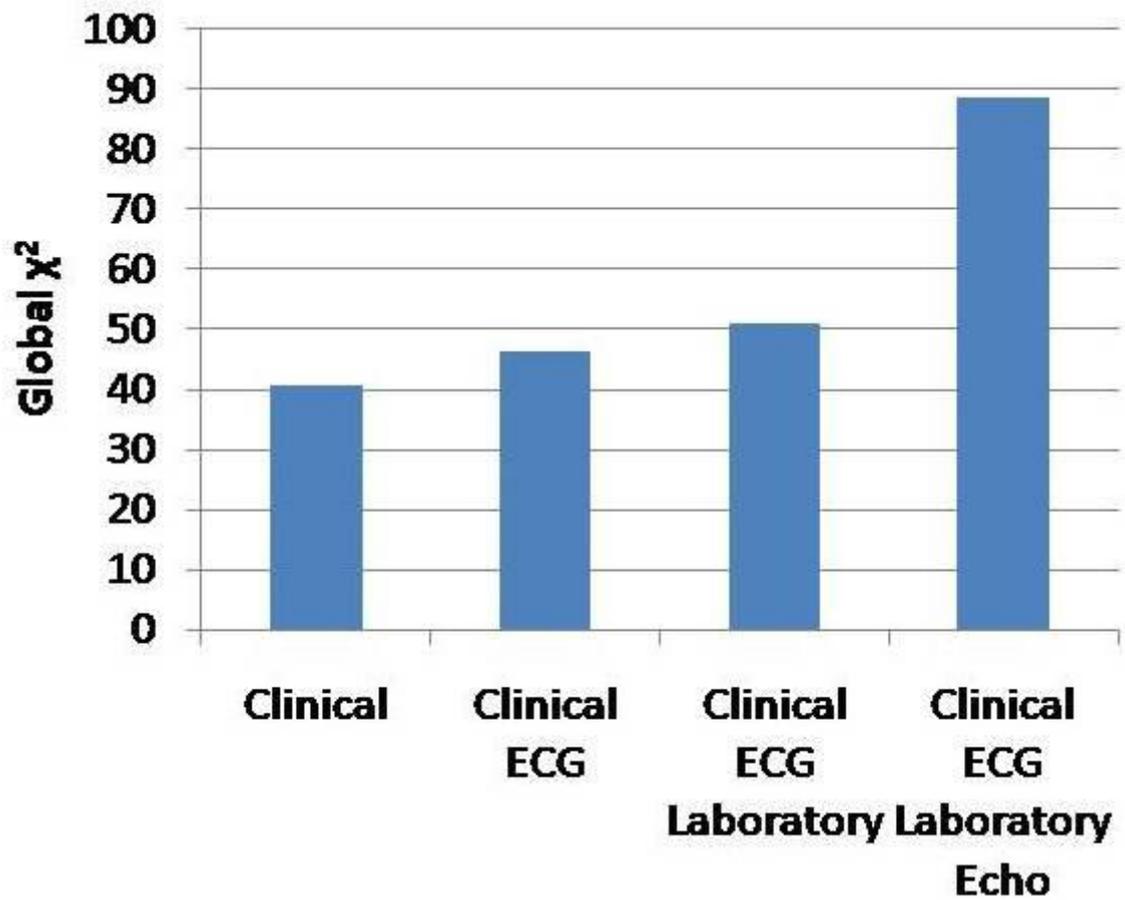
TABLES

Table 1. Clinical and demographics characteristics of the study population

Variables	Overall population (n = 227)	Patients with major complications (n=59)	Patients without major complications (n=168)	P value
Age (years)	66.2 ± 12.2	67.5 ± 14.5	65.8 ± 11.4	0.372
Age ≥ 75 years	65 (28.6)	25 (42.4)	40 (23.8)	0.011
Female gender	205 (90.3)	54 (91.5)	151 (89.9)	0.804
Body surface area (m^2)	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1	0.054
Medical History				
Hypertension	137 (60.4)	33 (55.9)	104 (61.9)	0.442
Hypercholesterolemia	88 (38.8)	20 (33.9)	68 (40.5)	0.438
Diabetes mellitus	25 (11.0)	10 (16.9)	15 (8.9)	0.096
Smoking	47 (20.7)	15 (25.4)	32 (19.0)	0.351
Menopause	180 (87.8)	46 (85.1)	134 (88.7)	0.477
Coronary artery disease	19 (8.4)	4 (6.8)	15 (8.9)	0.787
Active cancer*	16 (8.0)	6 (11.3)	10 (6.8)	0.376
Chronic obstructive pulmonary disease*	19 (9.5)	6 (11.3)	13 (8.9)	0.593
Presenting features				
Chest pain	161 (70.9)	27 (45.8)	134 (79.8)	< 0.001
Chest pain and dyspnea	30 (13.2)	15 (25.4)	15 (8.9)	0.003
Dyspnea	26 (11.5)	11 (18.6)	15 (8.9)	0.057
Others symptoms	10 (4.4)	6 (10.2)	4 (2.4)	0.021
Systolic blood pressure (mmHg)	131.1 ± 25.6	129.6 ± 32.6	131.6 ± 23.1	0.606
Diastolic blood pressure (mmHg)	77.4 ± 12.8	76.7 ± 14.1	77.7 ± 12.4	0.619
Heart rate (bpm)	84.8 ± 16.1	88.8 ± 20.5	83.4 ± 14.1	0.031
Presence of identifiable trigger events	187 (82.4)	48 (81.4)	139 (82.7)	0.843
Emotional trigger	133 (58.6)	31 (52.5)	102 (60.7)	0.286
Physical trigger	54 (23.8)	17 (28.8)	37 (22.0)	0.190
Serum				
Troponin I (ng/ml)	0.9 (0.3-2.0)	0.7 (0.3-1.6)	0.9 (0.3-2.2)	0.691
CK-MB (ng/ml)	19.7 (8.2-35)	18.5 (8.1-31)	20 (8.2-37.9)	0.401
BNP** (pg/ml)	806.8 ± 181.3	856.0 ± 207.0	790.0 ± 169.4	0.047
Hemoglobin (g/dl)	12.9 ± 1.5	12.8 ± 1.5	12.9 ± 1.5	0.596
GFR (ml/min)	70.2 ± 21.5	66.4 ± 25.2	71.6 ± 19.5	0.118
CRP (mg/dl)	12.6 (6.5-26.4)	13 (6.1-27.5)	12.5 (6.5-26.2)	0.938
ECG features at admission				
Isolated STE	72 (31.7)	15 (25.4)	57 (33.9)	0.258
STE with TWI	72 (31.7)	21 (35.6)	51 (30.4)	0.516
Non-STE	53 (23.3)	15 (25.4)	38 (22.6)	0.721
Isolated TWI	30 (13.2)	8 (13.6)	22 (13.1)	1.000
Prolonged QTc-interval	99 (43.6)	23 (39.0)	76 (45.2)	0.447
Left ventricular morphology				
Apical ballooning	175 (77.1)	42 (71.2)	133 (79.2)	0.213
Midventricular ballooning	41 (18.1)	12 (20.3)	29 (17.3)	0.694
Basal ballooning	11 (4.8)	5 (8.5)	6 (3.6)	0.159
Involvement of ≥4 coronary territories	204 (89.9)	57 (96.6)	147 (87.5)	0.047
Length of hospitalization (days)	7 (5-10)	9 (5-12.2)	6 (5-9)	0.002

Continuous normally distributed variables are mean ± SD. Categorical variables are n (%). Continuous non-normally distributed variables are median (interquartile range). *Data were available for 199 patients (53 with major complications). *Data were available for 157 patients (40 with major complications).

BNP = brain natriuretic peptide; CK-MB = creatine kinase-MB; CRP = C-reactive protein; ECG = electrocardiography; GFR = glomerular filtration rate; STE = STsegment elevation; TWI = T-wave inversion.

Table 2. Overall complications

Major complications	
Acute heart failure	45 (19.6)
Cardiogenic shock	18 (7.8)
Cardiac death	4 (1.7)
Other cardiac events	
Ventricular tachycardia/fibrillation	11 (4.8)*
Stroke	3 (1.3)
Apical thrombosis	3 (1.3)
Supraventricular tachycardia	1 (0.4)
Atrial fibrillation	15 (6.6)
Syncope	1 (0.4)

Values are n (%). *Nine patients had prolonged QTc intervals ($p = 0.012$).

Table 3. Echocardiographic findings on admission

Variables	Overall population (n = 227)	Patients with major complications (n=59)	Patients without major complications (n=168)	P value
LV end-diastolic volume (ml)	91.9 ± 22.7	97.3 ± 22.6	89.7 ± 22.5	0.051
LV end-systolic volume (ml)	57.3± 15.2	63.3 ± 15.7	54.8 ± 14.3	0.001
Indexed LV end-diastolic volume (ml/ m^2)	53.8 ± 14.3	60.3 ± 13.5	51.3 ± 13.8	0.002
Indexed LV end-systolic volume (ml/ m^2)	33.3 ± 9.1	39.1 ± 9.2	31.0 ± 8.1	<0.001
Diastolic IV septal thickness (mm)	12.1 ± 3.0	12.3 ± 3.4	12.0 ± 2.9	0.471
LV ejection fraction (%)	37.5 ± 5.2	35.1 ± 5.9	38.4 ± 4.6	<0.001
Wall motion score index	1.8 ± 0.2	1.9 ± 0.2	1.7 ± 0.2	<0.001
Left atrial volume (ml)	43.7 ± 8.2	47.4 ± 7.4	42.1 ± 8.1	<0.001
E peak velocity (cm/s)	75.2 ± 18.0	83.8 ± 20.0	71.7 ± 15.9	<0.001
A peak velocity (cm/s)	72.6 ± 21.1	68.0 ± 26.8	74.5 ± 18.2	0.081
E/A ratio	1.0 (0.7-1.3)	1.2 (0.7-1.9)	0.9 (0.7-1.2)	<0.001
DTE (ms)	202.0 ± 55.9	181.1 ± 54.0	209.3 ± 54.9	0.011
e' peak velocity (cm/s)	7.0 ± 2.3	6.2 ± 2.1	7.3 ± 2.3	0.007
E/e' ratio	11.0 ± 4.0	13.5 ± 4.3	9.9 ± 3.3	<0.001
sPAP (mmHg)	40.3 ± 10.4	47.4 ± 12.3	38.0 ± 9.2	<0.001
TAPSE (mm)	19.2 ± 3.2	19.4 ± 2.9	19.6 ± 3.3	0.709
Right ventricular area change (%)	38.7 ± 7.1	34.3 ± 8.1	40.1 ± 5.8	<0.001
Moderate to severe MR	49 (21.5)	29 (49.1)	20 (11.9)	<0.001
LV outflow tract obstruction	29 (12.8)	14 (23.7)	15 (8.9)	0.006
Right ventricular involvement	33 (14.5)	17 (28.8)	16 (9.5)	0.001

Continuous normally distributed variables are mean ± SD. Continuous non-normally distributed variables are median (interquartile range). Categorical variables are n (%). DTE = mitral E-wave deceleration time; E/A = mitral early diastolic velocity (E, cm/s) and late diastolic velocity (A, cm/s) ratio; E/e' = ratio of mitral E peak velocity and averaged e' velocity; IV = interventricular; LV = left ventricular; MR = mitral regurgitation; sPAP = pulmonary artery systolic pressure; TAPSE = tricuspid annular plane systolic excursion.

Table 4. Echocardiographic findings at short term follow-up

Variables	Overall population (n = 227)	Patients with major complications (n=59)	Patients without major complications (n=168)	P value
LV end-diastolic volume (ml)	86.2 ± 22.3	89.7 ± 23.7	84.8 ± 21.7	0.229
LV end-systolic volume (ml)	38.2± 11.0	39.8 ± 11.1	37.5 ± 10.9	0.271
Indexed LV end-diastolic volume (ml/ m^2)	49.9 ± 13.3	53.0 ± 16.9	48.7 ± 11.7	0.145
Indexed LV end-systolic volume (ml/ m^2)	21.8 ± 6.1	23.5 ± 6.4	21.3 ± 5.9	0.108
LV ejection fraction (%)	55.5 ± 7.1	54.7 ± 7.1	55.8 ± 7.1	0.319
Wall motion score index	1.1 (1-1.3)	1.1 (1-1.3)	1.1 (1-1.3)	0.753
Left atrial volume (ml)	41.5 ± 7.9	45.1 ± 7.1	40.0 ± 7.7	<0.001
E peak velocity (cm/s)	67.5 ± 15.1	74.8 ± 17.4	64.5 ± 13.1	0.002
A peak velocity(cm/s)	84.6 ± 19.5	80.4 ± 25.1	86.7 ± 16.7	0.151
E/A ratio	0.7 (0.6-0.9)	0.8 (0.6-1.3)	0.7 (0.6-0.8)	0.001
DTE (ms)	230 (190-254)	217 (175-252)	239 (196-261.2)	0.851
e' peak velocity (cm/s)	9.3 ± 2.0	7.9 ± 1.8	9.8 ± 1.8	<0.001
E/e' ratio	7.1 ± 2.2	9.1 ± 2.5	6.3 ± 2.2	<0.001
sPAP (mmHg)	28. ± 7.1	30.8 ± 7.3	28. ± 6.9	0.027
TAPSE (mm)	21.1 ± 2.8	21.8 ± 2.3	20. ± 2.9	0.032
Right ventricular area change (%)	41.4 ± 3.8	40.4 ± 4.0	41.8 ± 3.7	0.032
Moderate to severe MR	10 (7.6)	5 (12.8)	5 (5.4)	0.162
LV outflow tract obstruction	3 (1.3)	0 (0.0)	3 (1.8)	0.570
Right ventricular involvement	2 (0.9)	1 (1.7)	1 (0.6)	0.453

Continuous normally distributed variables are mean ± SD. Continuous non-normally distributed variables are median (interquartile range). Categorical variables are n (%). Abbreviations as in Table 3.

Table 5. Hazard ratio (95% CI) for the major adverse events (acute heart failure, cardiogenic shock, and in-hospital mortality) in univariate and multivariate models.

Variables	Wald Chi-square	p-value	HR	95% CI	Wald Chi-square	p-value	HR	95% CI
Age ≥ 75	7.162	0.007	2.353	1.257-4.403	4.270	0.039	2.818	1.055-7.529
Heart rate	4.492	0.034	1.020	1.001-1.038				
Chest pain with dyspnea	9.552	0.002	3.477	1.578-7.664				
BNP	3.385	0.049	1.002	1.000-1.004				
LVEF	15.398	< 0.001	0.892	0.842-0.944	18.400	<0.001	0.923	0.890-0.958
E/e' ratio	23.345	< 0.001	1.266	1.150-1.393	6.410	0.011	1.131	1.028-1.244
sPAP	23.549	< 0.001	1.086	1.050-1.122				
Mod. to severe MR	23.532	< 0.001	5.916	2.885-12.133	5.049	0.025	3.254	1.163-9.109
RV involvement	11.957	0.001	3.845	1.792-8.250				
LVOT obstruction	7.992	0.005	3.173	1.425-7.067				

BNP: brain natriuretic peptide; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract; MR: mitral regurgitation; RV: right ventricular; sPAP: pulmonary artery systolic pressure.