Additional prognostic value of 2D Right ventricular speckle tracking strain for prediction of survival in heart failure and reduced ejection fraction: A comparative study with cardiac Magnetic Resonance.

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Structured Abstract

Objectives

To compare the prognostic value of 2-dimensional (2D) right ventricular (RV) speckle tracking (STE) against Cardiac Magnetic Resonance (cMR) RV ejection fraction (EF) and feature tracking (FT) and conventional echocardiographic parameters on overall and cardiovascular survival in patients with heart failure and reduced ejection fraction (HF-rEF).

Background.

Prior works showed that RV systolic function predicts prognosis in HFrEF. 2D-RVSTE had recently been proposed as new echocardiographic method to evaluate RV dysfunction.

Methods.

266 patients with HF-rEF (mean LVEF 23±7%, age 60±14 years; 29% female) underwent RV function assessment using cMR and 2D echocardiography and were followed for a primary endpoint of overall death and secondary endpoint of CV death.

Results.

Average cMR-RVEF was 42%±15%, average STE-RVGLS was -18.0% ±4.9% average cMR-FT-RVGLS was -11.8±4.3%). After a median follow-up of 4.7 years, 102 patients died, 84 of CV cause. RVEF, FT-RVGLS, TAPSE, FAC and STE-RVGLS were significant univariate predictors of overall and cardiac death. In multivariate cox regression, age, ischemic etiology, diabetes, NYHA class III-IV, and beta blocker treatment were independent clinical predictors of overall mortality. cMR-RVEF ($\chi 2$ to enter=3.9, $p<0.05$), FT-RVGLS ($\chi 2$ to enter 3.7, $p=0.05$), FAC ($\chi 2$ to enter 6.2, $p=0.02$), and TAPSE ($\chi 2$ to enter=4.9, $p=0.04$) provided additional prognostic value over these baseline parameters, but the additional predictive value of STE-RVGLS ($\chi 2$ to enter=10.8, $p<0.001$) was significantly ($p<0.05$) higher than the other tests. Additional Hazard ratio [95% confidence interval] to predict overall mortality was 2.5 [1.6;3.9] for STE-RVGLS<-19%, 2.15 [1.34-3.43] for TAPSE>15 mm. 1.6 [1.02-2.49] for FAC>39% and 1.93 [1.25-2.99] for RVEF>41% and 1.87 [1.10-3.19] for cMR-FT-RVGLS<-15%.

Conclusion.

2D RVGLS provides strong additional prognostic value to predict overall and cardiovascular mortality in HF-rEF, with higher predictive value than cMR-RVEF, cMR-FT-RVGLS, TAPSE or FAC. This supports use of STE-RVGLS to identify higher risk HFrEF patients.

Key Words: Speckle Tracking Echocardiography, CMR, Heart Failure, Survival

Abbreviations

cMR: Cardiac Magnetic Resonance
EF: Ejection Fraction
eSPAP: estimated systolic pulmonary artery pressure
FAC : Fractional Area Change
FT: Feature Tracking
FWLS: Free wall longitudinal strain
GLS : Global longitudinal strain
HFrEF : Heart failure with reduced ejection fraction
LGE: late gadolinium enhancement
LV: Left Ventricle
RV: Right Ventricle
STE: Speckle tracking echocardiography
TAPSE: Tricuspid annulus plane systolic excursion

Introduction

Right ventricular (RV) systolic dysfunction has been recognized as an important predictor of outcome in heart failure (HF) (1-5). While cardiac magnetic resonance (cMR) derived RV ejection fraction (EF) is currently considered the gold standard technique for RV evaluation, echocardiography is more readily available in daily practice. Yet, accurate echocardiographic assessment of RV function remains challenging. Indeed, because of the complex shape of the RV there is actually no single RV echocardiographic parameter universally accepted for assessment of global right ventricular systolic function. Due to less angle dependency than conventional RV parameters(6), two-dimensional Speckle tracking echocardiography (2D STE) derived-RV myocardial global (RVLS) and free wall longitudinal strain (RVFWLS) have recently been proposed to evaluate RV dysfunction(7). However, so far no study has evaluated whether the prognostic value of these new approaches equals cMR derived RVEF to identify HF patients at higher risk of mortality.

Therefore, the aim of this study was to estimate the prognostic significance of 2DSTE-RVGLS and FWLS, in patients with heart failure and reduced ejection fraction (HF-rEF) in direct comparison to cMR RVEF and Feature tracking (FT) and to conventional echocardiographic parameters such as TAPSE and FAC. Accordingly, we prospectively studied 266 patients with HFrEF using Cox survival analysis to assess the independent additional prognostic value of 2DSTE vs RVEF-CMR to predict overall and cardiovascular survival over baseline clinical and echocardiographic data.

Materials and Methods

Study population

From a prospective registry, we identified consecutive patients with LVEF < 35% who underwent cMR between 2002 and 2015 in our institution. Inclusion criteria were stable chronic heart failure patients in sinus rhythm and available transthoracic echocardiography (TTE) within 40 days of CMR. Exclusion criteria were image quality precluding RV strain analysis, hemodynamic instability, atrial fibrillation or flutter, moderate and severe primary valve disease. Secondary cardiomyopathies and cardiotoxic chemotherapy, severe chronic kidney disease defined as a Modification of Diet in Renal Disease formula (MDRD) <30 ml/min/1.73 m2 and patients with life expectancy <1 year due to other comorbidities were also excluded. 266 patients satisfied the inclusion criteria (**Figure 1**) and constituted the final study population. The study protocol was approved by the IRB of the institution.

Clinical Data

Patient's medical history and treatment were prospectively recorded. Other information was retrieved from medical files and from review of hospital records. The etiology of heart failure was considered ischemic or non-ischemic on the basis of documented prior myocardial infarction or angiographically proven coronary artery disease according to Felker et al(8).

TTE Echocardiography

Standardized complete TTE exams acquired according to established guidelines using Sonus 7500 or iE33 ultrasound systems (Philips Medical Systems, Andover, MA, United States) equipped with a 3.5/1.75-MHz phased-array transducer and stored on a XCELERA 2.1 PACS server were analyzed off-line by a single observer (LH) blinded to follow-up clinical and CMR data. TAPSE and FAC were measured according to established guidelines on 4 chamber views oriented to the RV. Estimated pulmonary systolic artery pressure (eSPAP) was calculated based

on the Bernouilli simplified equation on continuous wave Doppler imaging of tricuspid regurgitation maximum jet velocity. Pulmonary hypertension was considered when eSPAP was >40 mmHg. LV and RV strains were computed using 2D-STE Tomtec software (4.6 version, Tomtec Unterschleissheim, Germany). Endocardial borders of the RV and LV were automatically tracked throughout the cardiac cycle by the software, with manual corrections if necessary. Images with poor quality tracking were excluded. LV peak global longitudinal strain (GLS) was computed by averaging four and two chambers view. For the RV we evaluated both peak systolic global RV longitudinal strain (RVGLS) and peak systolic free wall longitudinal strain (RV FWLS). The average frame rate of the clips for RV and LV strain analysis was 47±11 frame rates per second.

CMR

CMR studies were acquired using a 1.5T or 3T systems (Intera CV and Achieva, Philips Medical Systems, Best, the Netherlands) as described before(9). Briefly, 10-12 consecutive short axis images covering the entire left ventricle, and respectively one 2- 3- and 4 chambers long-axis cine SSFP images were acquired for assessment of myocardial function. 10-15 minutes after injection of 0.2 mmol/kg gadolinium based contrast, identical prescriptions of short- and long-axis slices were acquired using a 2D- or 3D inversion recovery sequence allowing for the assessment of myocardial viability.

CMR studies were analyzed using the freely available software Segment version 2.2 (*http://segment.heiberg.se*) (10) by one experienced observer (BG). Right and left ventricular volumes and EF were computed from the short-axis cine images by semi-automatically tracing the endo- and epicardial contours in the end-diastolic (ED) and end-systolic (ES) phases. Values were indexed to the body surface area. Presence and extent of late gadolinium enhancement

(LGE) was evaluated visually and quantified with a semi-automated algorithm, as previously reported(9). FT-RVGLS was performed using the same Segment software in 4 chamber cine view,

Follow-up

Patients were prospectively followed until April 2017 by phone contact with the patients, their relatives, or their physician. All deaths were recorded and categorized as cardiac or noncardiac. Cardiac death was defined as death attributable to congestive heart failure (i.e. death preceded by acute worsening or exacerbation of heart failure) myocardial infarction, sudden death (i.e. unexpected, unwitnessed, or witnessed death in absence of other apparent causes) or occurring after cardiac revascularization. **The primary endpoint** was overall death. The **secondary endpoint** was cardiovascular (CV) death. Since time to heart transplantation is not only determined by the patient status, but also by organ availability, heart transplantation was not considered an event, but patients were censored at the date of the procedure.

Statistical analysis.

Statistical analyses were performed using R software (version 3.3.2). All tests were 2 sided and p value <0.05 was considered statistically significant. Continuous variables were expressed as mean ± one standard deviation (SD), categorical variables as counts and percentages. Hazard Ratios (HR) were expressed as mean and 95% confidence intervals (CI). Interobserver and intraobserver reproducibility of measurement of RV function was evaluated in 15 randomly selected patients using intraclass correlation coefficient (ICC) and Bland-Altman analysis with computation within-subject coefficient of variation. Our study had 90% power with $\alpha=0.05$ to detect a twofold increase of hazard of death (ie 60% vs 78% survival at 5 years) in low vs high median of RV function. Continuous and categorical variables of baseline characteristics of

patients were compared among tertiles of RVGLS using ANOVA or $\chi 2$ test respectively. The correlation between CMR-derived RVEF vs echocardiographic measures of RV function was examined using Pearson's correlation coefficient. To determine independent predictor of the primary endpoint, uni and multivariate Cox proportional hazard models were used. For the secondary endpoint we used a proportional subdistribution hazards' regression model accounting for competing risk (crr function in cmprsk package).All clinical, echocardiographic and MR parameters were proposed for inclusion in the univariate model. Then a stepwise backward model including all significant ($p<0.10$) univariate clinical correlates of survival was used to construct a clinical baseline model predicting either overall or cardiovascular survival. To assess the potential additive prognostic value of RVGLS and the others RV parameters we evaluated the ability of all the RV parameters to improve the prediction of death from this baseline model by comparing the additional increase of chi square of the combined model over the baseline model. Finally we determined the cutoff values of RVEF, RVGLS, FAC and TAPSE by the highest hazard ratios to predict survival, and computed Kaplan-Meyer survival graphs adjusted for baseline covariates as well as incremental $\chi 2$ values over baseline model. Models were compared using likelihood tests.

Results

Baseline characteristics of patients

Median delay between cMR and echo was 7 (IQR 1-15) days. FT cMR was not feasible in 16 patients because of poor tracking. The mean age of HF patients were 60±14 years and 71% were male. Etiology of heart failure was ischemic in 51% of patients and 56% were in New York Heart association (NYHA) class III or IV. Mean LV-EF was 23±7%. Table 1 shows characteristics of the study population according to tertiles of STE-RVGLS. There were no

significant differences in age or sex between the tertiles. By contrast, patients with a more impaired RV strain had a higher resting heart rate, more advanced NYHA class, higher diuretic and aldosterone blocking drug use, lower LVEF, higher indexed LV ventricular volumes, estimated systolic pulmonary artery pressure (eSPAP), E/a ratio and more severe tricuspid regurgitation than those with less altered systolic RV strain. Also CMR-derived RV volumes and FT-RVGLS were higher, while RVEF, TAPSE and FAC were significantly lower in patients with the most depressed STE-RVGLS.

Correlation of RV function by echocardiography vs CMR

Table 2 shows correlation of RV functional parameters by echocardiography vs cMR RVEF. All RV echocardiographic parameters correlated significantly (r between 0.60 and 0.65) with CMR-derived RVEF. Surprisingly, cMR FT-RVGLS correlated however only moderately with cMR-RVEF ($r=0.45$, $p<0.001$) and with STE-RVGLS ($r=0.47$, $p<0.001$). A moderate correlation between CMR-derived RVEF and LVEF was also observed ($r=0.55$ $p<0,001$) whereas the correlation with LV GLS ($r=-0.34$; $p<0.001$) was weak. Finally, STE-RVFWLS and STE-RVGLS were highly correlated among each other (0.85, $p<0.001$), but average STE-RVFWLS was significantly greater than STE-RVGLS.

Events at Follow-up

Follow-up was 100% complete for a median duration of 4.7 years. During follow-up 102 patients died, 84 of cardiovascular causes: 3 postoperatively, 38 suddenly, 3 of stroke, 7 of cardiogenic shock, and 33 of heart failure. 18 patients died of non-cardiac causes (10 cancers, 2 Alzheimer, 5 sepsis, 1 COPD). 21 patients underwent heart transplantations and were censored. Accordingly, 102 patients reached the primary endpoint of all-cause death and 84 the secondary endpoint of CV death.

Predictors of overall and CV survival

Table 3 shows the univariate cox regression analysis for the primary endpoint of overall survival. Age, ischemic etiology, diabetes, NYHA functional class III or IV, estimated systolic pulmonary artery pressure (eSPAP)> 40mmHg, STE and FT-RVGLS, RVFW, RV-FAC, TAPSE, E/A and E/é ratio, MDRD, beta blocker treatment and cMR-derived RV indexed volumes and RVEF were associated with overall mortality. LV-GLS and cMR-LGE presence or scar burden >2% were associated with mortality. However LV-EF was not predictive of either overall or cardiovascular mortality in univariate analysis.

Multivariate models for overall and cardiovascular survival are shown in **Tables 4 and 5,** respectively. Age, ischemic cardiomyopathy, diabetes, NYHA class > II and betablocker treatment were independent predictors of overall death. CV death was predicted by the same parameters and, in addition, eSPAP>40 mmHg and MRDR. Baseline models using these parameters were constructed to predict overall and CV death. cMR-RVEF, FT-RVGLS, STE-RVGLS, RV-FWLS andRV-FAC were found to have significant additional prognostic value for overall and cardiovascular mortality over these baseline models. TAPSE was found to only provide additional value for overall, but not for cardiovascular mortality. The predictive value of RV-GLS and RV-FWLS was similarly good (p=NS), and significantly (p<0.001) higher than of cMR RVEF and FT-RVGLS. By contrast, cMR-LVEF did not have additional prognostic value for overall (X2 to improve=1.78, p=0.18) or cardiovascular mortality (X2 to improve 1.6, p=0.19). LVGLS had incremental value for cardiovascular (X2 to improve 6.3, HR 1.10[1.03 ;1.19], p=0.008) but not overall mortality (X2 to improve 0.4, p=0.51). Also, since LGE presence or scar burden >2% was highly correlated with ischemic etiology (kappa=0.64, p<0.001), they did not have additional prognostic value over baseline models for either

endpoints. Optimal cutoff values of RV parameters yielding the highest additional HR for overall survival were 41% for RVEF 41%, 39% for RV-FAC 39%, 15 mm for RV-TAPSE 15 mm, -15% for FT-RVGLS and -19% for RV-GLS and RVFWLS. **Figure 2** shows Kaplan Meier survival graphs for adjusted overall and CV mortality stratified by these cutoff values. It clearly demonstrates that both overall and cardiovascular survival significantly declined with worsening RV function irrespective of the method used. **Figure 3** compares the additional $\chi 2$ statistic value of different RV parameters by cMR and echocardiography to increase predictive value for overall and cardiovascular survival. while **Figure 4** shows the additional hazard ratio of these tests. RVEF>41%, FT-RVGLS<-15 %, TAPSE>15 mm and FAC>39% significantly improved prediction of overall and cardiovascular mortality over baseline clinical variables to similar amounts. However RVGLS<-19% had the highest incremental predictive value and provided the highest increase in hazard ratio for both overall and CV mortality. Notably, the incremental value of RVGLS was significantly higher than that of RVFWLS for overall mortality.

Reproducibility of RVLS measurements

Reproducibility of RV measurements is shown in **Table 6**. All measurements had good intra- and interobserver reproducibility.

Discussion

The principal findings of our study were:

1) RV dysfunction assessed either by cMR or echocardiography, predicts overall and cardiovascular survival with significant additional value over baseline clinical parameters such as age, NYHA class, ischemic etiology, betablocker treatment, renal function and eSPAP.

2) RVGLS and RVFWLS were strongly correlated, but RVGLS had slightly better predictive value than RVFWLS.

3) Most importantly, the predictive value of echocardiography derived 2DSTE-RV GLS was superior to CMR-derived RVEF, FT-RVGLS, TAPSE and FAC for both overall and CV mortality

Prognosis of HFrEF and the importance of RV function

Heart failure (HF) is associated with significant morbidity and mortality. However individual patients may have highly variable prognosis. Therefore it is important to identify patients at higher risk for mortality who might benefit from more intensive monitoring and therapy. Several prognostic markers of death and/or HF hospitalization have been identified and various clinical risk scores have been proposed in patients with HF-rEF(11,12). Our present study not onlyconfirmed the role of several of these previously described risk factors, in particular age, NYHA class, renal function and pulmonary hypertension, but also demonstrated significant additional prognostic value of RV dysfunction over and above these well-known clinical parameters both in ischemic or non-ischemic HFrEF patients. Importantly, the additional prognostic value of all the RV parameters was significantly higher and independent of LV systolic functional parameters, which lose their prognostic value in these HF-rEF patients with severely depressed LV function because of the tight range of LVEF and LVGLS values in these patients.

This is consistent with several recent studies demonstrating that RV dysfunction assessed using different techniques such as echocardiography (4,13,14), radionuclide ventriculography(1,2,15,16), right heart catheterization (17) and CMR (3,18) is a key determinant of outcome in HFrEF patients. Indeed, in HFrEF, RV dysfunction can be caused from several mechanisms such as postcapillary pulmonary hypertension, RV myocardial ischemia, ventricular interdependence due to septal dysfunction. It may also represent a common

disease process affecting cardiomyocytes in both ventricles(17,19). RV dysfunction is thus likely not only a marker of more severe LV disease and higher pulmonary pressures, but also directly contributes to less efficient cardiac performance, more severe exercise intolerance and heart failure.

Assessment of RV function by echocardiography

Despite its importance, the complex geometrical anatomy of the RV makes the assessment of RV systolic function by cardiac imaging techniques difficult. Initial works to evaluate RV function relied on radionuclear angiography, but CMR has emerged as the gold standard for RV function. Indeed, CMR is ideally suited for the assessment of the RV because it allows high-resolution time-resolved visualization of the complex anatomical shape of the right ventricle in different directions. However, it has limited availability and high costs. Echocardiography is more widely used for clinical assessment of patients with heart failure, and would be better suited for HFrEF risk stratification . Yet, echocardiography has certain limitations for the assessment of RV systolic function in particular due to the to the complex RV shape, and restricted RV echo-windows. Hence no optimal parameter for RV functional measurements by echocardiography has been identified. Indeed, 2D-echo-derived RV ejection fraction and volumes were found to be poorly reliable and are currently not recommended for clinical use or standard reference in research. TAPSE has been proposed as a simple measurement of longitudinal function but may not accurately reflect global RV function. Nevertheless it has the important advantage of being easily measureable even when image quality is poor. RV FAC may better reflect RV function but dependents on image plane, requiring complete visualization of the entire RV structure. Also it was found to have high inter- and intraobserver variability and poor performance when endocardial definition is suboptimal. In prior works, the evidence for both FAC and TAPSE as

predictive parameter was conflicting(14). In our study, however, both TAPSE and FAC were significantly correlated to cMR-derived RVEF. While FAC was talented to predict overall and cardiovascular outcome , TAPSE was not found to predict cardiovascular mortality over baseline parameters.

More recently 2D-STE has been proposed as better method for evaluation of RV function by echocardiography(20). It has the advantage of being an automated user-independent parameter, which may more accurately reflect RV function than FAC or TAPSE. Indeed several studies demonstrated that 2D RV strain has prognostic value in HF (21-24). However, most of these studies did not evaluate the additional prognostic value over clinical and echocardiographic parameters(21-25) or against cMR RVEF. Importantly, we demonstrated that both 2D RVGLS and FWLS were the most reliable echocardiographic measures of RV function, surpassing FAC and TAPSE for predicting overall and cardiovascular mortality. Surprisingly, STE-RVGLS was also superior to cmR-FT-RVGLS. This might be explained by differences in softwares, less temporal resolution for FT-cMR than for STE and the fact that FT does not rely on anatomical speckles to track.. An important debate in RV strain methodology is whether GLS or FW should be evaluated. The majority of studies evaluated the prognostic value of RVFWLS, based on the fact that the intraventricular septum (IVS) is a constituent part of the LV, and that RVFWLS would thus more closely evaluate RV function than RVGLS. In favor of this, Cameli and al. (26) showed that RVFWLS had the highest diagnostic accuracy to predict a depressed RV stroke work index in a simultaneous echocardiographic-catheterization study. Conversely, through the IVS, the LV contributes 20-40% to RV systolic pressure(27), and canine studies demonstrated that the inactivation of the IVS leads to a significant decrease in right ventricular function and that the reduction of RVFWLS function does not affect RVEF in the presence of a preserved

IVS(28). In our study RVGLS and FW were strongly correlated, but RVGLS had a slightly better reproducibility and higher predictive value for overall mortality than RVFWLS. This contrasts with findings in isolated pulmonary hypertension(29) and probably reflects the more important role of LV-RV interaction in HFrEF than in isolated pulmonary hypertension. Importantly both 2D RVGLS and RVFWLS were found to have even higher prognostic value for overall and cardiovascular mortality than CMR-derived RVEF and FT-RVGLS.

Clinical implications

Our study suggests that RV assessment should be part of the comprehensive evaluation and stratification of HFrEF patients in order to identify patients at higher risk for bad outcome. More importantly our study strengthens and expands previous studies by showing that RV-GLS by echocardiography may provide similarly or even better risk prognostic value than cMR derived RVEF with high intra and interobserver reproducibility. This simple echocardiographic measurement, which can easily be performed at bed site, could thus avoid less accessible and more costly cMR exams for risk stratification. Although RV-GLS was the best echocardiography method for prognosis, the fact that other RV parameters had also good predictive value, suggests that in clinical practice, simpler parameters such as TAPSE could be suitable alternatives when the image is too poor for RV strain analysis.

Limitations

Although our study was a large cohort of homogenous and consecutive patients with short interval between echocardiography and cMR, it is limited by being a single centre retrospective observational study of patients referred to cMR for evaluation of cardiac function, with a potential referral reference bias and by the fact that both tests were not performed simultaneously. We excluded 13% of patients due to poor image quality precluding strain

analysis. Indeed a significant limitation of RV strain remains the need for high quality images and frame rate dependency as well as limited standardization and intervendor variability with wide range of normal value. In prospective design higher frame rate and better image quality would certainly be obtained. We also excluded subjects with comorbidities such as atrial fibrillation and severe chronic kidney disease (CKD) at the time of examination, which are strongly associated with mortality in these patients and therefore our study findings may not apply to this populations. Also FT and STE Strain analysis were performed with two different vendor- softwares and specific cut off values reported in this study may not apply to other softwares or other populations. Also, we assessed only the longitudinal function of the RV by 2D strain, since longitudinal shortening, rather than circumferential deformation, determines RVEF. Despite the fact that RV radial shortening plays also a role to the overall RVEF, radial strain is difficult to measure especially in the thin walled RV and the reproducibility is extremely low(30). Finally, brain natriuretic peptide, right-sided index of myocardial performance (RIMP) and peak tissue Doppler systolic velocity (S'wave) were not available for the entire study and could not be evaluated in models of outcome prediction.

Conclusion

Our study clearly establishes that 2STE-RV strain is a strong independent predictor of overall and cardiovascular mortality, providing additional prognostic value over clinical parameters in patients with HFrEF. Importantly, both 2STE-RV GLS and FWS were found to have higher predictive value than cMR RV-EF, RV-FTRVGLS, FAC and TAPSE. This supports systematic evaluation of right ventricular function by 2DST for risk stratification in HFrEF patients.

CLINICAL PERSPECTIVES

Competency in Medical Knowledge

In this retrospective study, comparing cMR and echocardiography, right ventricular dysfunction was found to be a strong independent predictor of overall and cardiovascular mortality in patients with HFrEF. The use of echocardiographic derived right ventricular global longitudinal strain was the most powerful echocardiographic parameter and had higher prognostic value than cMR derived RV- EF, suggesting that systematic evaluation of RV function by 2D STE could be important for risk stratification in HFrEF patients.

Translational Outlook

The retrospective design in a single center, as well as the use of a single vendor software for right ventricular strain analysis remain a limitation. Additional clinical studies should confirm the value of 2D-STE in such populations in prospective, multicenter design and using different softwares to allow more general recognition of this method for risk stratification of HFrEF patients.

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Figure Legends

Figure 1: Flowchart of patient inclusion.
Flowchart of patient inclusion and exclusion criteria. HF-rEF indicates Heart failure reduced ejection fraction; AF, atrial fibrillation; MDRD, Modification of Diet in Renal Disease

Figure 2: Kaplan-Meyer Event-Free Survival curves.
Kaplan-Meyer event-free Kaplan Meyer adjusted overall and cardiovascular survival stratified by optimized cutoff value of RVEF<41% cMR-FT RVGLS<15% , TAPSE<15 mm , FAC<39% and RV-GLS<19% . Adjustments were made for age, ischemic etiology, NYHA class, Diabetes, betablocker treatment, pulmonary hypertension and MDRD

Figure 3: Chi square statistic of Models.
Chi square statistic of baseline model for overall (white) and cardiovascular (grey) mortality andof different RV functional tests stratified by optimized cutoff value to predict overall and cardiovascular mortality over baseline parameters**.** Values indicate the additional Chi square of the different models. * indicates p<0.05 vs other tests # indicates p<0.05 vs FAC, ¶ indicates p<0.05 vs RVGLS vs RVWFS. Statistical comparisons by likelihood ratio tests.

Figure 4: Additional Hazard ratios
Adjusted additional Hazard ratios of different right ventricular parameters to predict a) overall b) cardiovascular survival over baseline clinical parameters.

Table 1: Clinical characteristics of HF-rEF patients according to tertiles of RV GLS

	Total population (n=266)	Tertile 1 RV GLS(n=89)	Tertile 2 RV GLS (n=88)	Tertile 3 RV GLS (n=89)	P-value
Clinical Characteristics					
Age (years)	**60 ± 14**	**60± 15**	**62 ± 14**	**59 ± 13**	**0.37**
Women (n. %)	**78 (29%)**	**28 (31%)**	**24 (27%)**	**26 (29%)**	**0.85**
ICM (n, %)	**135 (51%)**	**53(60%)**	**43 (49%)**	**39(44%)**	**0.088**
BMI (kg/m^2)	**26 ± 5**	**25 ± 4**	**26 ± 5**	**26 ± 5**	**0.55**
BSA (m^2)	**1.84 ± 0.21**	**1.82 ± 0.2**	**1.85 ± 0.2**	**1.85 ± 0.2**	**0.79**
MAP (mmHg)	**86± 13**	**87± 13**	**85± 13**	**85± 13**	**0.52**
Heart rate(bpm)	**80± 19**	**73± 19**	**80 ± 16**	**87± 19**	**<0.001**
NYHAIII-IV (n. %)	**146 (55%)**	**23(27%)**	**54(61%)**	**68(76%)**	**<0.001**
Comorbidities					
HTA (n. %)	**121(46%)**	**45 (51%)**	**42 (48%)**	**34(38%)**	**0.24**
Diabetes Mellitus (n. %)	**63 (24%)**	**14 (16%)**	**19 (22%)**	**28 (33%)**	**0.12**
Ever smoker (n. %)	**164(62%)**	**48 (54%)**	**52(59%)**	**64(72%)**	**0.09**
HistMI (n. %)	**105 (39%)**	**39(44%)**	**346(41%)**	**30(33%)**	**0.37**
HistPCI (n. %)	**39 (15%)**	**15 (17%)**	**16 (18%)**	**8 (9%)**	**0.19**
HistCABG (n. %)	**13 (5%)**	**3 (3%)**	**7 (8%)**	**3(3%)**	**0.56**
Blood results					
MDRD (ml/min/1.73m^2)	**71 ± 22**	**76 ± 26**	**68 ± 20**	**68 ± 18**	**0.033**

Sodium (mg/dl)	**138 ± 4**	**138 ± 3**	**138 ± 4**	**137 ± 5**	**0.007**
Hemoglobin(g/dl)	**12.24±1.8**	**13.3± 1.4**	**13.3± 1.8**	**13.6± 2.12**	**0.27**
Medication. n (%)					
Aspirine	**182(68%)**	**62(70%)**	**61(69%)**	**59(66%)**	**0.8**
ACE/ARB	**262 (98%)**	**88 (99%)**	**88 (100%)**	**86 (97%)**	**.17**
Beta blockers	**238(89%)**	**78(88%)**	**78(89%)**	**82(92%)**	**0.62**
Digitale	**7(3%)**	**2 (2%)**	**3 (4%)**	**2(2%)**	**0.86**
Aldosterone blockers	**192 (72%)**	**52(58%)**	**66 (75%)**	**74(83%)**	**<0.001**
Diuretics	**182 (68%)**	**44(49%)**	**66(75%)**	**72(81%)**	**<0.001**
Statin	**139(52%)**	**47(53%)**	**52(59%)**	**40(45%)**	**0.24**
Antiarrythmic drugs	**41(15%)**	**13(15%)**	**11(13%)**	**17(19%)**	**0.34**
Echocardiographic measurements					
STE-RV-GLS(%)	**-18.0 ± 4.9**	**-23.± 2**	**-18 ± 2**	**-12 ± 2**	**By design**
STE-RV-FWLS(%)	**-18.7 ± 6.6**	**-25 ± 5**	**-18 ± 4**	**-13 ± 4**	**<0.001**
TAPSE(mm)	**18 ± 5**	**21 ± 4**	**18 ± 4**	**16 ± 4**	**<0.001**
RV-FAC(%)	**37 ± 12**	**46 ± 9**	**36 ± 9**	**28 ± 10**	**<0.001**
eSPAP(mmHg)	**34 ± 11**	**28± 9**	**36 ± 11**	**36± 12**	**<0.001**
eSPAPS>40mm Hg	**62(23%)**	**10(11%)**	**20 (23%)**	**32 (36%)**	**<0.001**
E/A ratio	**1.5 ± 1.0**	**1.2 ± 1.25**	**1.6 ± 0.9**	**1.95 ± 0.85**	**<0.001**
E/e' ratio	**19 ± 14**	**14 ± 8**	**19 ± 9**	**22 ± 14**	**<0.001**
Moderate/severe TR (n.%)	**26(10%)**	**1(1%)**	**8(9%)**	**17(19%)**	**<0.001**

LV GLS(%)	**-10.5 ± 3.3**	**-12± 3**	**-11 ± 3**	**-9± 3**	**<0.001**
cMR measurements					
LV-EDVi (ml/m²)	**155 ± 49**	**143± 37**	**159 ± 57**	**164± 49**	**0.009**
LV-ESVi (ml/m²)	**121 ± 47**	**106 ± 34**	**125 ±52**	**134 ± 48**	**0.0001**
LV-EF (%)	**23 ± 7**	**27 ± 6**	**23 ± 7**	**19 ± 7**	**<0.001**
RV-EDVi (ml/m²)	**86 ± 33**	**69 ± 18**	**89 ± 32**	**100 ± 38**	**<0.001**
RV-ESVi (ml/m²)	**53 ± 33**	**33 ± 15**	**57± 30**	**710± 37**	**<0.001**
RV-EF (%)	**42 ± 15**	**54 ± 11**	**38 ± 12**	**32 ± 13**	**<0.001**
RV-EF>45% (n. %)	**110(41%)**	**72 (81%)**	**25 (28%)**	**13(15%)**	**<0.001**
FT-RVGLS	**-11.8±4.3**	**-14.1±4.3**	**-11.8±4.2**	**-9.7±3.3**	**<0.001**
LV Scar (n. %)	**156(59%)**	**52(58%)**	**56(64%)**	**48(54%)**	**0.43**
Scar burden (%)	**8± 9**	**10± 10**	**9± 10**	**6± 7**	**0.57**

Across-group P value is for the difference across the tertiles of RVGLS(lower, middle and upper tertiles) by the Anova test.

ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin receptor blocker; BMI: body mass index; BSA: body surface area; CABG: coronary artery bypass graft; EDVi: indexed end-diastolic ventricular volume; ESVi: indexed end-systolic ventricular volume; EF: ejection fraction; eSPAP: estimated systolic pulmonary artery pressure; FAC: fractional area change; FWLSL: free-wall longitudinal strain; GLS: global longitudinal strain; Hist: History of; HTA: arterial hypertension; ICM: ischemic cardiomyopathy; LV: left ventricular; MI: myocardial infarction; MAP: mean arterial pressure; MDRD: Modification of Diet in Renal Disease

formula; MR: mitral regurgitation; PCI: percutaneous coronary intervention; RV: right ventricular; TASPE: Tricuspid annular plane systolic excursion; TR: tricuspid regurgitation;

Table 2: Pearson's linear correlations of parameters with CMR derived RVEF

	Pearson's correlation (R)	**p value**
RV-FAC	**0.65**	**<0.001**
TAPSE	**0.62**	**<0.001**
STE-RV-GLS	**-0.62**	**<0.001**
STE-RV-FWLS	**-0.57**	**<0.001**
cMR-LVEF	**0.55**	**<0.001**
LV-GLS	**0.34**	**<0.001**

Abbreviations as in table 1

Table 3. Univariate predictors of overall death.

	Alive N=164	Dead N=102	HR (95% CI)	P-value
Clinical characteristics				
Age(years)	**56 ± 10**	**66 ± 11**	**1.52[1.03;1,07]**	**<0.001**
Women (n,%)	**54 (33%)**	**24 (24%)**	**0.66[0.41;1.04]**	**0.07**
ICM (n,%)	**60 (36%)**	**73 (73%)**	**2.2[1.42;3.46]**	**<0.001**
HTA (n,%)	**66 (40%)**	**55 (54%)**	**1.39[0.95;2.06]**	**0.09**
Diabetes Mellitus (n,%)	**25 (15%)**	**38 (37%)**	**2.19[1.46;3.28]**	**<0.001**
NYHA III-IV (n,%)	**84 (51%)**	**62 (61%)**	**1.56[1.05;2.33]**	**0.03**
Medications (n,%)				
Aspirin	**98 (60%)**	**83 (82%)**	**1.87[1.12;3.118]**	**0.02**
Beta-blockers	**153 (93%)**	**85 (83%)**	**0.48[0.29;0.82]**	**0.006**
Diuretics	**107 (65%)**	**75 (74%)**	**1.71[1.10;2.67]**	**0.02**
Laboratory test				
MDRD (ml/kg/1.73m²)	**74 ± 23**	**66 ± 19**	**0.98[0.97;0.99]**	**<0.001**
Echocardiographic measurements				
LV-GLS (%)	**-11 ± 3**	**-10 ± 3**	**1.06[0.99;1.13]**	**0.05**
STE-RV-GLS (%)	**-18 ± 5**	**-17 ± 5**	**1.06[1.1;1.11]**	**0.002**
STE-RV-FWLS (%)	**-19 ± 7**	**-18 ± 6**	**1.06[1.02;1.09]**	**0.001**

TAPSE (mm)	**19 ± 4**	**18 ± 5**	**0.95[0.91;0.99]**	**0.011**
RV-FAC (%)	**37 ± 12**	**36 ± 11**	**0.985[0.96;0.99]**	**0.021**
eSPAP>40mmHg	**32 (18%)**	**30 (36%)**	**1.81[1.19;2.04]**	**0.005**
E/a ratio	**1.5 ± 1.1**	**1.6 ± 0.8**	**1.36[1.12;1.67]**	**0.002**
E/e'	**18±8**	**20±10**	**1.03 [1.01;1.06]**	**0.012**
cMR measurements				
RV-EVDi (ml/m²)	**84 ± 3**	**89 ± 33**	**1.007[1.001;1.014]**	**0.01**
RV-ESVi (ml/m²)	**52 ± 33**	**56 ± 32**	**1.008[1.002;1.015]**	**0.005**
RV-EF (%)	**42 ± 15**	**41 ± 16**	**0.98[0.97;0.99]**	**0.03**
FT-RVGLS (%)	**-12.0±4.1**	**11.7±4.5**	**1.06 [1.01;1.11]**	**0.015**
LV-EF (%)	**23 ± 7**	**23 ± 7**	**0.98[0.9;1.01]**	**0.16**
Presence of LV scar (n. %)	**83 (51%)**	**73 (72%)**	**1.578[1.02;2.4]**	**0.04**
Scar burden > 2%	**71 (43%)**	**71 (70%)**	**1.84 [1.2; 2.8]**	**0.004**

All parameters were tested, but only parameters with $p<0.10$ were reported.

CI: Confidence Interval; HR: Hazard Ratio. All other abbreviations as in table 1

Table 4: Multivariate Cox analysis for prediction of overall death

Parameter	Partial HR	X^2	P value
Age	1.05 [1.03;1.07]	24.2	<.0001
Ischemic Etiology	1.85 [1.17;2.93]	6.9	.008
Diabetes	1.95 [1.29;2.96]	9.9	.002
NYHA class III-IV	1.75 [1.16;2.64]	7.0	.008
Betablocker R/	0.51[0.30;0.86]	6.4	.011
Combined Baseline model		**58.2**	**<0.001**

Parameter	X2 to improve	Partial HR	p
cMR-RVEF	3.9	0.98[0.97;1.00]	0.05
cMR-FT-RVGLS	3.7	1.05 [0.99;1.10]	0.05
STE-RVGLS*	10.8	1.08[1.03;1.13]	<0.001
STE-RVFWLS¶	9.3	1.06[1.02;1.10]	0.002
RV-FAC	6.2	0.97[0.96;0.99]	0.02
TAPSE	4.1	0.95[0.91;0.99]	0.04

*p<0.05 vs FAC, TAPSE and cMR-RVEF, ¶ p<0.05 vs TAPSE and cMR-RVEF

Abbreviations as in Table1

Table 5. Multivariate subdistribribution hazard model for prediction of cardiovascular death corrected for subdivision

Parameter	Partial HR	X^2	P value
Age	1.03 [1.01;1.06]	10.5	<0.007
Ischemic Etiology	2.52 [1.529;4.18]	10.1	<0.001
Diabetes	1.52 [0.97;2.41]	4.8	.07
NYHA class II-IV	1.62 [1.01;2.61]	4.5	.05
Betablocker R/	0.41 [0.23;0.73]	8.2	.002
eSPAPs>40 mm	1.80 [1.14;2.82]	5.4	.01
MDRD	.99 [1.01;1.00]	3.1	.05
Combined Baseline model		**56.9**	**<0.001**

Parameter	X2 to improve	Partial HR	p
cMR-RVEF	4.2	0.98[0.97 ;0.99]	0.0394
cMR-FT-RVGLS	7.5	1.09 [1.04 ;1.14]	<0.001
STE-RVGLS*	10.6	1.09[1.03 ;1.15]	0.001
STE RVFWLS¶	8.4	1.06[1.02 ;1.10]	0.001
RV-FAC	6.9	0.97[0.95 ;0.99]	0.001
TAPSE	1.3	0.97[0.93 ;1.01]	0.18

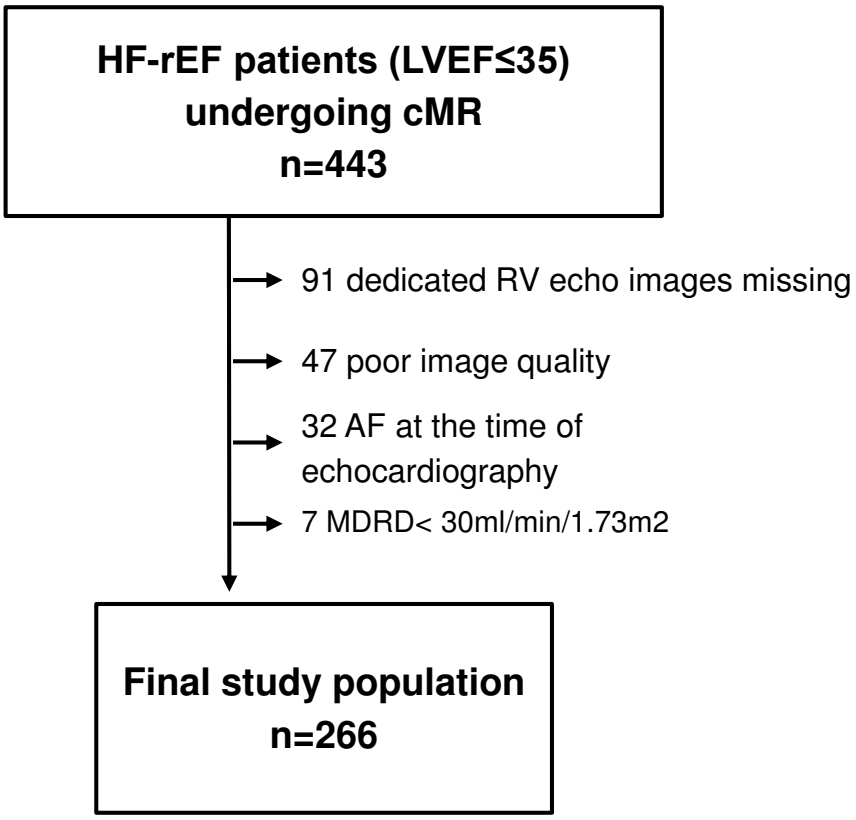
*p<0.05 vs FAC, TAPSE and cMR-RVEF, ¶ p<0.05 vs TAPSE and cMR-RVEF

Abbreviations as in Table1

Table 6: Reproducibility of measurements

	Intra-observer Reproducibility		Inter-observer Reproducibility	
	CV [95% CI]	ICC	CV [95% CI]	ICC
cMR RV-EF	13.1% [3.4;18.3]	0.96	11.3% [6.5;14.7]	0.94
TAPSE	4.7% [3.3;5.8]	0.98	18.3% [5.7;25.3]	0.82
RV-FAC	7.3% [2.7;10]	0.91	13.8% [9.8;16.9]	0.76
STE-RVGLS	3.6% [2.0;4.8]	0.98	9.6% [6.3;12.0]	0.86
STE-RVFWLS	13.9% [10.4;16.8]	0.80	15.6% [9.0;20.1]	0.82

CI: confidence interval; CV: coefficient of variation; ICC: Intra-class correlation coefficient. Other Abbreviations as table 1.


HF-rEF patients (LVEF≤35)
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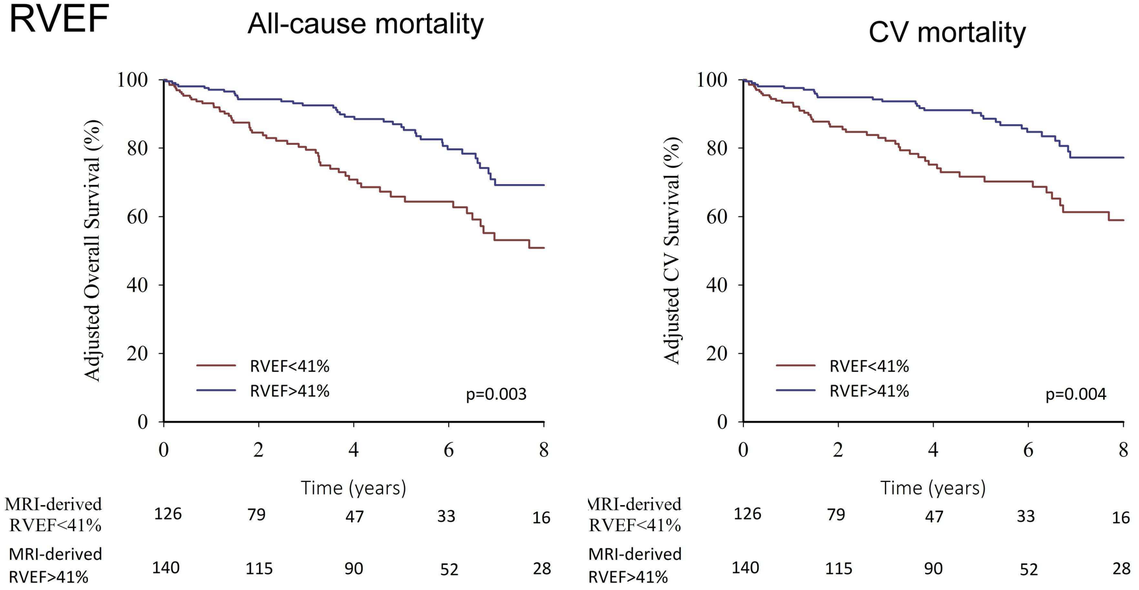
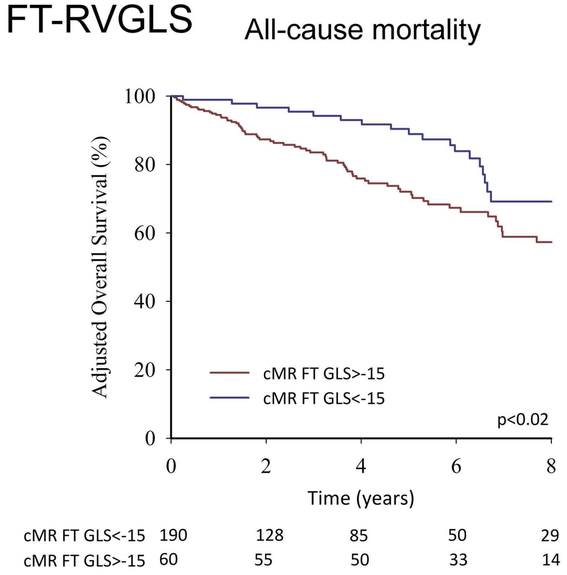
Final study population
n=266

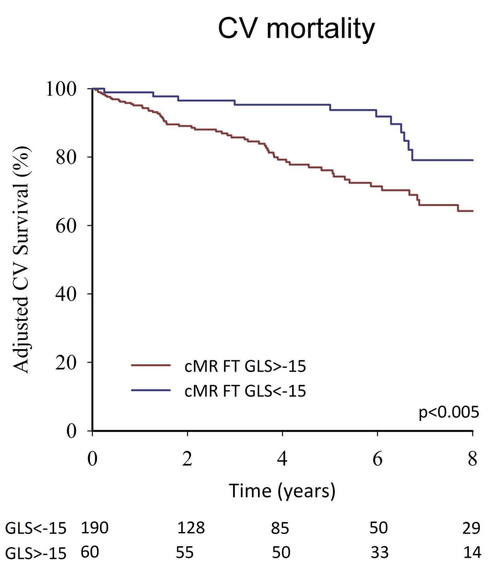
cMR

RVEF



FT-RVGLS





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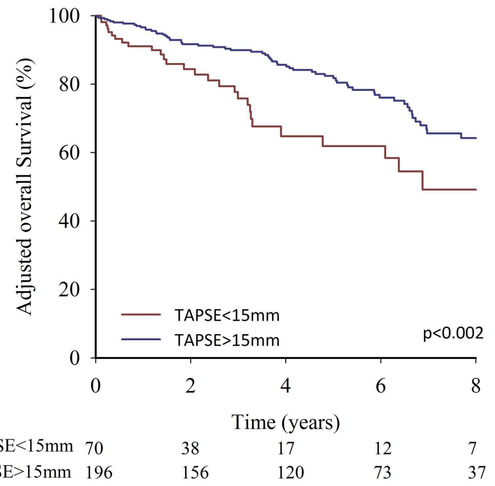
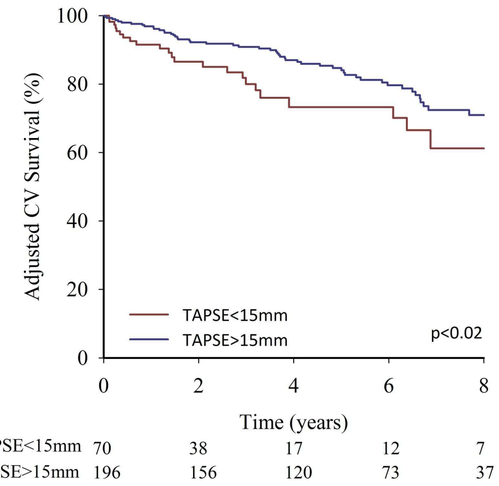
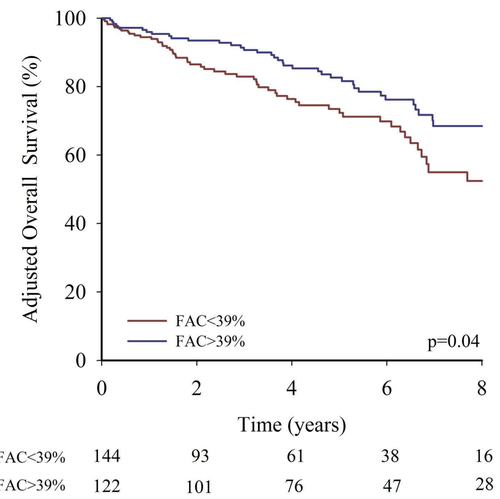
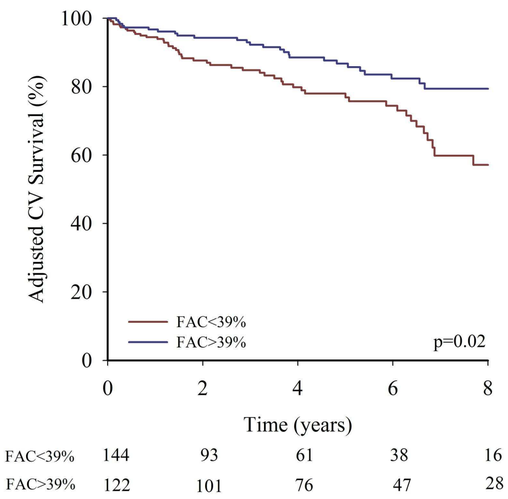
TAPSE





FAC





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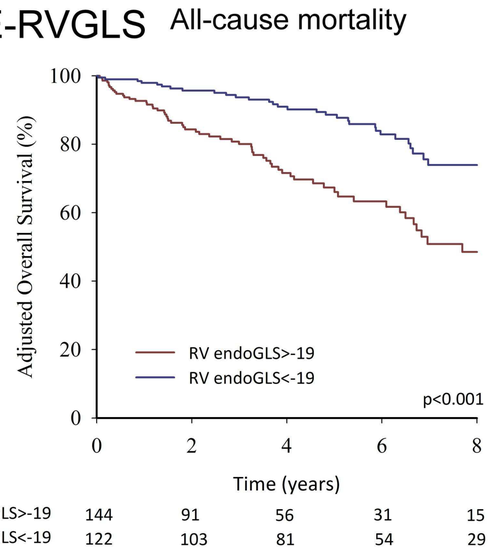

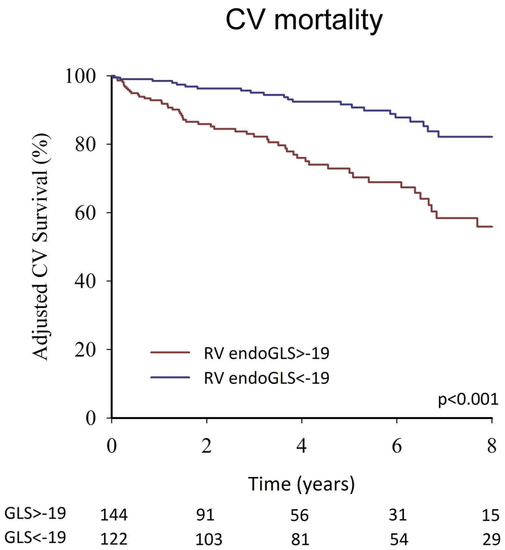

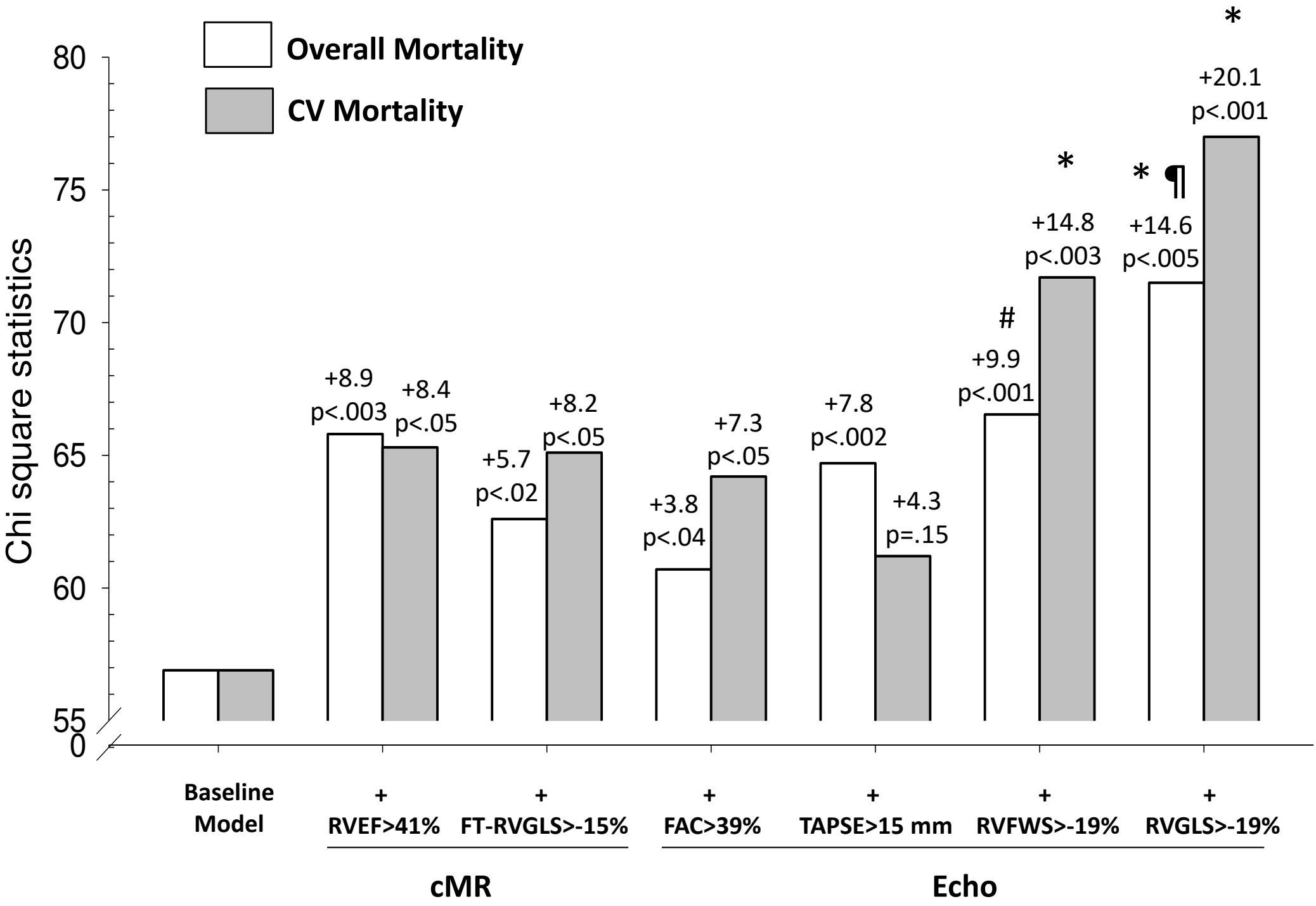
Overall Mortality
CV Mortality
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75
70
65
60
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p<.003
+8.4
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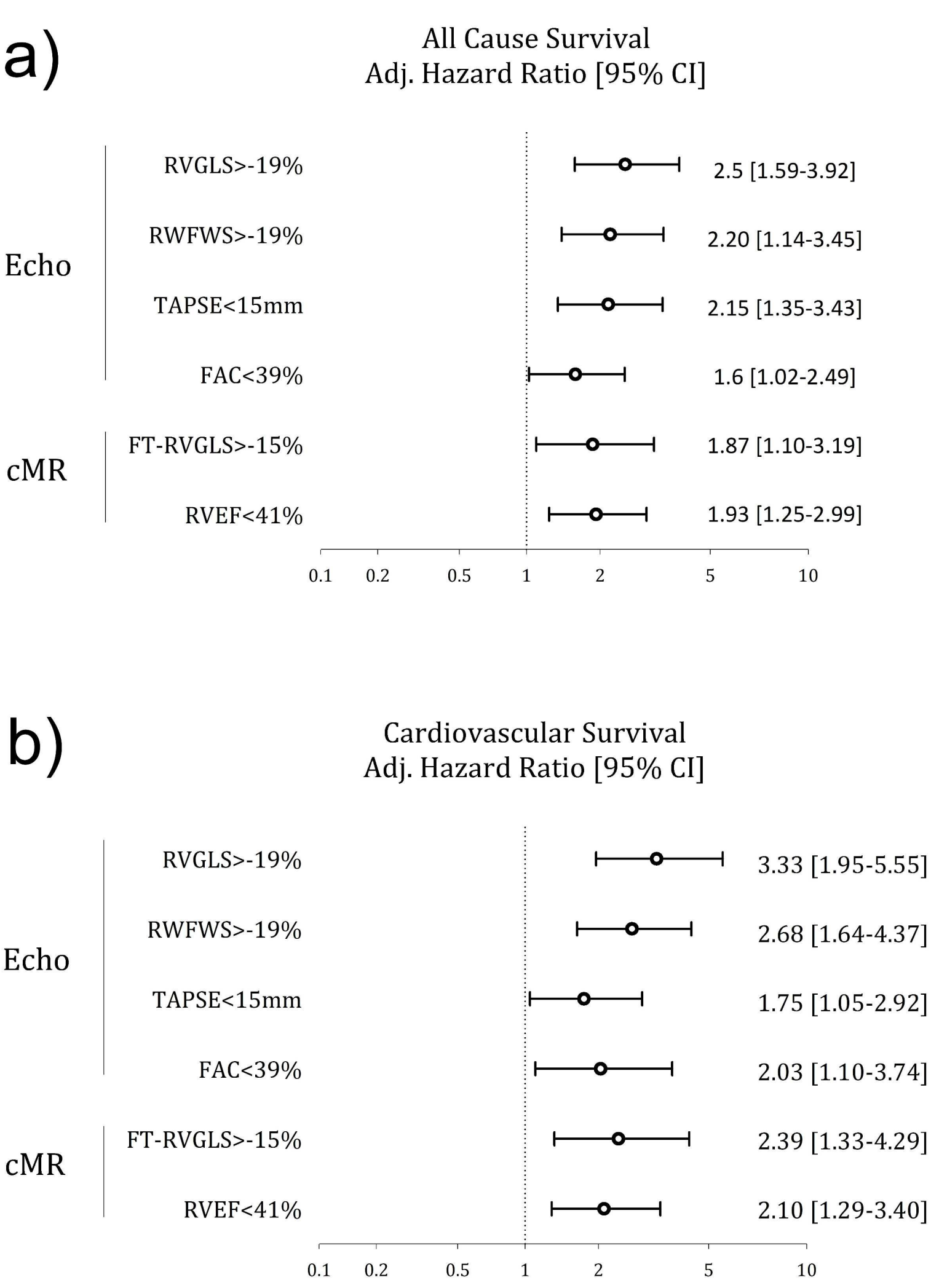
+5.7
p<.02
+8.2
p<.05
+3.8
p<.04
+7.3
p<.05
+7.8
p<.002
+4.3
p=.15
+9.9
p<.001
#
+14.8
p<.003
*
+14.6
p<.005
* ¶
+20.1
p<.001
*
Baseline Model
+ RVEF>41%
+ FT-RVGLS>-15%
+ FAC>39%
+ TAPSE>15 mm
+ RVFWS>-19%
+ RVGLS>-19%
cMR
Echo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All Cause Survival
Adj. Hazard Ratio [95% CI]
Echo
cMR
RVGLS>-19%
RWFWS>-19%
TAPSE<15mm
FAC<39%
FT-RVGLS>-15%
RVEF<41%
2.5 [1.59-3.92]
2.20 [1.14-3.45]
2.15 [1.35-3.43]
1.6 [1.02-2.49]
1.87 [1.10-3.19]
1.93 [1.25-2.99]
0.1
0.2
0.5
1
2
5
10
b)
Cardiovascular Survival
Adj. Hazard Ratio [95% CI]
Echo
cMR
RVGLS>-19%
RWFWS>-19%
TAPSE<15mm
FAC<39%
FT-RVGLS>-15%
RVEF<41%
3.33 [1.95-5.55]
2.68 [1.64-4.37]
1.75 [1.05-2.92]
2.03 [1.10-3.74]
2.39 [1.33-4.29]
2.10 [1.29-3.40]
0.1
0.2
0.5
1
2
5
10

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