Significant Disagreement Between Conventional Parameters and 3D Echocardiography-Derived Ejection Fraction in the Detection of Right Ventricular Systolic Dysfunction and Its Association With Outcomes

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Aims: Conventional echocardiographic parameters such as tricuspid annular plane systolic excursion (TAPSE), fractional area change (FAC), and free-wall longitudinal strain (FWLS) offer limited insights into the complexity of right ventricular (RV) systolic function, while 3D echocardiography-derived RV ejection fraction (RVEF) enables a comprehensive assessment. We investigated the discordance between TAPSE, FAC, FWLS, and RVEF in RV systolic function grading and associated outcomes.

Methods: We analyzed two- and three-dimensional echocardiography data from 2 centers including 750 patients followed up for all-cause mortality. Right ventricular dysfunction was defined as RVEF <45%, with guideline-recommended thresholds (TAPSE <17 mm, FAC <35%, FWLS >−20%) considered.

Results: Among patients with normal RVEF, significant proportions exhibited impaired TAPSE (21%), FAC (33%), or FWLS (8%). Conversely, numerous patients with reduced RVEF had normal TAPSE (46%), FAC (26%), or FWLS (41%). Using receiver-operating characteristic analysis, FWLS exhibited the highest area under the curve of discrimination for RV dysfunction (RVEF <45%) with 59% sensitivity and 92% specificity. Over a median 3.7-year follow-up, 15% of patients died. Univariable Cox regression identified TAPSE, FAC, FWLS, and RVEF as significant mortality predictors. Combining impaired conventional parameters showed that outcomes are the worst if at least 2 parameters are impaired and gradually better if only one or none of them are impaired (log-rank $P < .005$).

Conclusion: Guideline-recommended cutoff values of conventional echocardiographic parameters of RV systolic function are only modestly associated with RVEF-based assessment. Impaired values of FWLS showed the closest association with the RVEF cutoff. Our results emphasize a multiparametric approach in the assessment of RV function, especially if 3D echocardiography is not available. (J Am Soc Echocardiogr 2024;37:677-86.)

Keywords: 2D echocardiography, 3D echocardiography, Right ventricular ejection fraction, Tricuspid annular plane systolic excursion, Free-wall longitudinal strain, Fractional area change

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Lawrence Rudski, MD, served as guest editor for this article.

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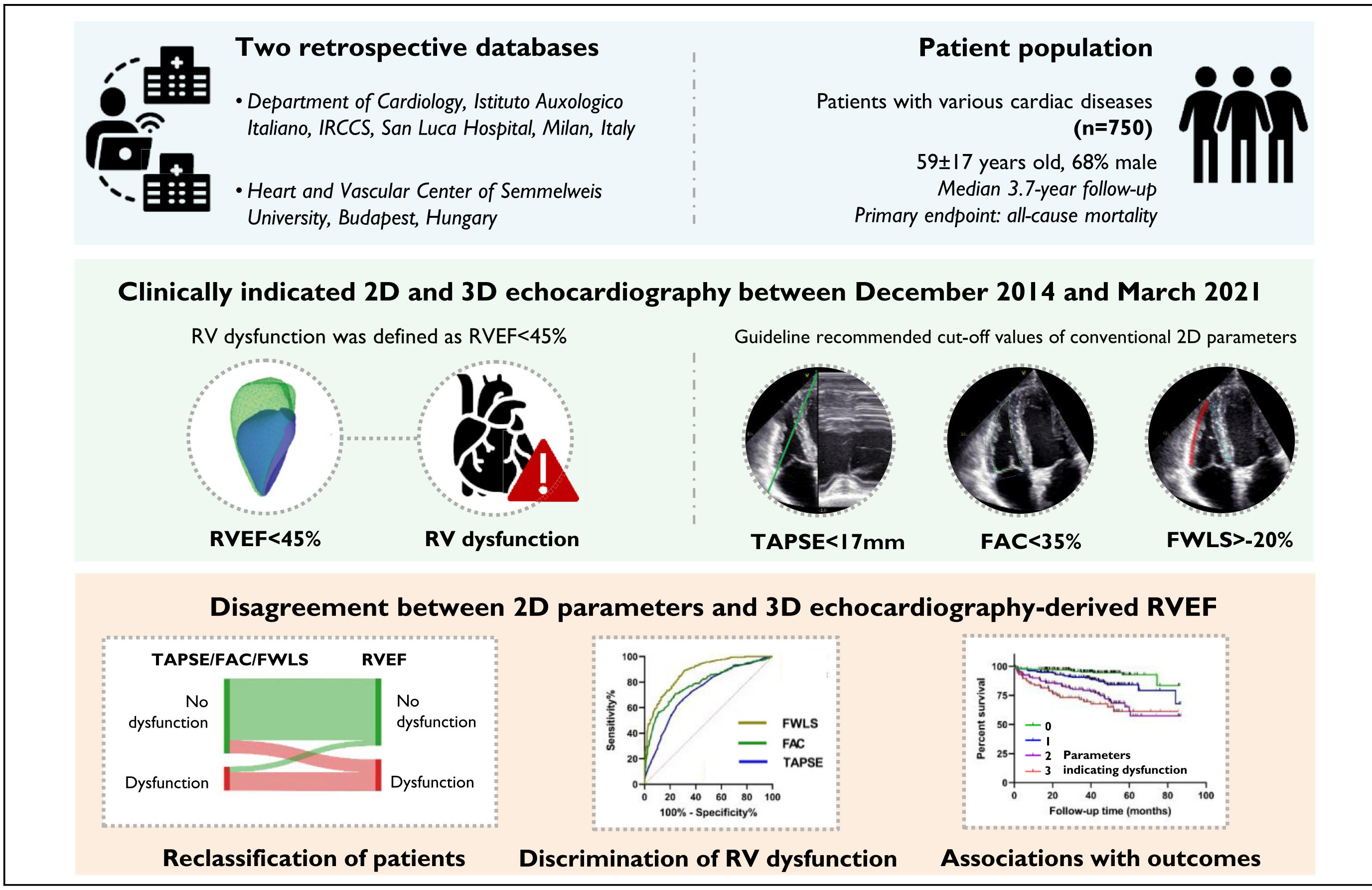
0894-7317

https://doi.org/10.1016/j.echo.2024.04.005



Central Illustration Outline and outcome measures of our study. *FAC*, Fractional area change; *FWLS*, free-wall longitudinal strain; *RV*, right ventricle; *RVEF*, right ventricular ejection fraction; *TAPSE*, tricuspid annular plane systolic excursion.

INTRODUCTION

The assessment of right ventricular (RV) systolic function is of paramount importance in the evaluation of various cardiovascular pathologies.[1] Conventional echocardiographic parameters, such as tricuspid annular plane systolic excursion (TAPSE), fractional area change (FAC), and free-wall longitudinal strain (FWLS), have long been recommended as standard measures to assess RV function.[2-4]

However, it is increasingly recognized that conventional echocardiographic parameters provide only a partial representation of the complex functional characteristics of the right ventricle (RV).[5] The RV exhibits unique anatomical and mechanical properties that set it apart from the left ventricle (LV), necessitating a comprehensive assessment of its function.[5] As such, relying solely on TAPSE, FAC, and FWLS, which explore mostly the longitudinal mechanics of the RV, may not fully capture the full spectrum of RV dysfunction and its potential impact on clinical outcomes.[3,4]

In recent years, three-dimensional (3D) echocardiography (3DE) has emerged as a promising imaging modality for the assessment of cardiac function, including the RV. Among the various 3DE-derived parameters, RV ejection fraction (RVEF) has demonstrated its utility as a reliable and reproducible measure of RV systolic function.[4,6,7] By leveraging the additional spatial information provided by 3DE, RVEF offers a more comprehensive evaluation of RV performance and may potentially overcome the limitations of conventional parameters.[5,8]

Given the potential discordance between conventional echocardiographic parameters and 3DE-derived RVEF in assessing RV systolic function, it becomes crucial to investigate the prevalence of such discrepancies and their impact on clinical outcomes. Understanding the divergence in RV systolic function grading by different approaches can play a significant role in patient management, prognostication, and therapeutic decision-making.

Given these considerations, the present study aims to explore the discordance between TAPSE, FAC, FWLS, and RVEF in diagnosing RV systolic function and its impact on clinical outcomes.

METHODS

Study Design and Population

Patients with various cardiac diseases who underwent clinically indicated two- and three-dimensional (2D and 3D) transthoracic echocardiography between December 2014 and March 2021 at the Department of Cardiology, Istituto Auxologico Italiano, IRCCS, Milan, Italy, and at the Heart and Vascular Center of Semmelweis University, Budapest, Hungary, were retrospectively identified.

The following inclusion criteria were used: (1) availability of recordings of both LV and RV full-volume datasets, (2) sufficient image quality and volume rate to perform LV and RV volumetric analysis; (3) availability of follow-up data. Protocol 2D and 3DE were performed on all patients. Image quality was judged subjectively (based on the

Abbreviations

2D = Two-dimensional

3D = Three-dimensional

3DE = Three-dimensional echocardiography

ACS = Acute coronary syndrome

AUC = Area under the curve

DCM = Dilated cardiomyopathy

EDAi = End-diastolic area index

EDVi = End-diastolic volume index

EF = Ejection fraction

ESAi = End-systolic area index

ESVi = End-systolic volume index

FAC = Fractional area change

FWLS = Free-wall longitudinal strain

HR = Hazard ratio

HTX = Heart transplant

ICD = Implantable cardioverter-defibrillator

LV = Left ventricle

ROC = Receiver-operating characteristic

RV = Right ventricle

RVEF = Right ventricular ejection fraction

RVSP = Right ventricular systolic pressure

SVi = Stroke volume index

TAPSE = Tricuspid annular plane systolic excursion

optimization of the pyramidal dataset for width and depth, the signal-to-noise ratio, the volume rate—ideally ≥20 volume per second—and the completeness of LV and RV endocardium visualization) and was graded on a scale from 1 to 5 (from poor to excellent). Poor-quality 3DE datasets were considered to have insufficient image quality and were not included in further analyses. Demographic and clinical data (age, weight, height, body surface area, body mass index, systolic and diastolic blood pressure, heart rate, cardiovascular risk factors, comorbidities, and medical history) were retrieved from the electronic clinical records of the hospital database. Written informed consent was waived because of the retrospective nature of the analysis. Our study protocol follows the Declaration of Helsinki, and it was approved by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics (approval no. 190/2020) and by the Ethics Committee of the Istituto Auxologico Italiano (approval no. 2021_05_18_13).

Two- and Three-Dimensional Echocardiography

Transthoracic echocardiographic examinations were performed on commercially available ultrasound systems (E9, E95, 4Vc-D probe, GE Vingmed Ultrasound; and EPIQ 7, X5-1 probe, Philips Medical Systems). A standard acquisition protocol consisting of 2D loops from parasternal, apical, and subxiphoid views was applied. Digitally stored datasets in raw-data format were analyzed offline using commercially available software packages in the different centers (EchoPAC BT12, GE Vingmed; and TomTec Imaging). Tricuspid annular plane systolic excursion, RV end-diastolic (EDA) and end-systolic area (ESA), FAC, and RV systolic pressure (RVSP) were measured according to current guidelines.[4]

Beyond conventional echocardiographic examination, ECG-gated full-volume 3D datasets reconstructed from 4 or 6 cardiac cycles optimized for the left or the right heart were obtained for further analysis on a separate workstation. Three-dimensional datasets focused on the left heart were processed using semiautomated, commercially available software packages (AutoLVQ, EchoPAC BT12, GE Vingmed; and 4D LV-Analysis 3, TomTec Imaging). We determined LV end-diastolic volume index (EDVi), end-systolic volume index (ESVi), and stroke volume index (SVi). Ejection fraction (EF) was also calculated to assess global LV function. Concerning the right heart, we quantified 3D RV EDVi, ESVi, SVi, EF, and septal and free-wall 2D longitudinal strain (FWLS) as well (4D RV-Function 2, TomTec Imaging). All echocardiographic measurements were performed locally in the framework of the clinical routine by attending physicians having at least 3 years of experience in advanced echocardiographic postprocessing (4-4 investigators from each center). This group of investigators previously reported good reproducibility for these measures.[9]

Study Outcomes

Our primary aim was to assess the classification differences between conventional echocardiographic parameters of the RV systolic function and 3DE-derived RVEF. Right ventricular systolic dysfunction was defined as RVEF <45%. Guideline-recommended cutoff values were used to indicate RV systolic dysfunction (i.e., TAPSE <17 mm, FAC <35%, FWLS >−20%).

Follow-up data (status [dead or alive], date of death) were obtained from clinical records, Hungary's National Health Insurance Database, and Italy's National Health Service Database. The primary end point of our study was all-cause mortality.

Statistical Analysis

Statistical analysis was performed using SPSS (ver. 25, IBM) and GraphPad Prism (ver. 9.5.1, GraphPad Software). Continuous variables are expressed as mean ± SD, whereas categorical variables are reported as frequencies and percentages. After verifying the normal distribution of variables using the Kolmogorov-Smirnov and Shapiro-Wilk tests, the clinical and echocardiographic characteristics were compared with unpaired Student *t* test or Mann-Whitney *U* test for continuous variables and chi-squared or Fisher's exact test for categorical variables, as appropriate. Multiple group comparisons (>2) were performed using one-way analysis of variance or Welch's analysis of variance and chi-squared or Fisher exact test, as appropriate. Follow-up duration was estimated using the reverse Kaplan-Meier method. Using univariable Cox regression, we identified factors associated with all-cause mortality. Survival of different groups based on their classification by conventional parameters was visualized via Kaplan-Meier curves and compared using log-rank tests. Cox proportional hazard models were used to compute hazard ratios (HRs) with 95% CIs between the groups. To demonstrate that RVEF has a superior prognostic power compared with the conventional RV parameters, we compared the Harrell C-indices (i.e., concordance indices) of the univariable Cox proportional-hazards models including 1 parameter (RVEF, FAC, FWLS, or TAPSE) at a time. After dichotomizing RVEF, FAC, FWLS, and TAPSE based on their guideline-defined cutoff values, their HRs for all-cause mortality were also calculated with 95% CIs using univariable Cox proportional-hazards models. Receiver-operating characteristic curves were constructed to investigate the discriminative power of guideline-recommended cutoff values of conventional parameters for RV systolic dysfunction assessed by RVEF. For the comparison of areas under the ROC curves (AUC), DeLong tests were performed using MedCalc Statistical Software (ver. 22.018, MedCalc Software). Sankey diagrams were constructed using SankeyMATIC

HIGHLIGHTS

- RV dysfunction cutoffs of 2D echo parameters are modestly associated with RVEF <45%.
- RVEF-based reclassification of RV dysfunction is associated with different outcomes.
- Impaired values of FWLS show the closest association with the RVEF cutoff.
- A multiparametric approach is the preferred option when 3D echo is not available.

(https://sankeymatic.com) to visualize the volume of reclassified patients caused by the discordance between conventional parameters and RVEF in identifying RV systolic dysfunction. A 2-sided *P* value of <.05 was considered statistically significant.

RESULTS

Baseline Clinical and Echocardiographic Characteristics and Their Association With Outcomes

A total of 750 Caucasian patients were included in this 2-center study (393 patients from the Department of Cardiology, Istituto Auxologico Italiano, IRCCS, Milan, Italy, and 357 patients from the Heart and Vascular Center of Semmelweis University, Budapest, Hungary). Initially, 906 patients were identified, of whom 156 patients (17%) were excluded. The reasons for exclusion were the unavailability of RV or LV 3DE full-volume datasets (42 patients), inadequate 3D image quality for RV or LV analysis (105 patients), irregular rhythm and stitching artifacts (8 patients), and duplication (1 patient). During the median follow-up time of 3.7 (interquartile range, 2.7-4.5) years, 112 (15%) patients died. Demographic and clinical characteristics of the study cohort and a comparison of patients according to outcome are presented in Table 1. A comparison according to centers is also available in Supplemental Table 1.

The most frequently observed comorbidities were hypertension (60%), dyslipidemia (46%), coronary artery disease (26%), and diabetes (20%). Patients who died were older, had a higher heart rate and a higher prevalence of diabetes and coronary artery disease, and more frequently underwent implantable cardioverter-defibrillator (ICD) implantation (Table 1); these conditions and comorbidities were also significant predictors of mortality using univariable Cox regression (Table 2). All included 2D and 3DE parameters of RV size and systolic function differed significantly between patients who stayed alive versus those who died during the follow-up (Table 1) and were also associated with all-cause mortality (Table 2).

The univariable Cox model including RVEF had the highest Harrell's C-index (RVEF, 0.729 [95% CI, 0.678-0.780]; FAC, 0.686 [95% CI, 0.631-0.741]; FWLS, 0.688 [95% CI, 0.637-0.739]; TAPSE, 0.664 [95% CI, 0.613-0.715]). When we compared the C-indices, RVEF exhibited superior prognostic power compared to FWLS ($P = .029$) and TAPSE ($P = .035$), while there was no significant difference compared to FAC ($P = .130$).

The HRs of the parameters dichotomized based on the guideline-defined cutoff values are presented in Supplemental Table 2. The greatest increase in the risk of all-cause mortality was observed if RV dysfunction was assessed using RVEF (HR [95% CI], 4.676 [3.169-6.900]; $P < .001$).

Free-wall longitudinal strain exhibited the highest discriminatory power for RV systolic dysfunction (AUC, 0.877 [95% CI, 0.852-0.902]; $P < .001$]), exceeding that of FAC (AUC, 0.787 [95% CI, 0.750-0.824]; $P < .001$]) and TAPSE (AUC, 0.729 [95% CI, 0.690-0.767]; $P < .001$]; Figure 1) with significant difference between all AUCs based on the DeLong tests (FAC vs FWLS $P < .001$; FAC vs TAPSE $P = .015$; FWLS vs TAPSE $P < .001$). Based on guideline-recommended cutoff values, sensitivity and specificity of discrimination for RV systolic dysfunction (RVEF <45%) were 55% and 79% for TAPSE, 76% and 67% for FAC, and 59% and 92% for FWLS on ROC analysis, respectively.

The clinical outcomes were the worst if at least 2 conventional echocardiographic parameters showed RV systolic dysfunction, and gradually better if only one or none of them was abnormal. All Kaplan-Meier curves differed significantly from each other (log-rank $P < .005$) except for the comparison between the curves of 2 and 3 impaired parameters (Figure 2). Hazard ratios of all-cause mortality in the different subgroups based on the number of conventional parameters indicating RV dysfunction are summarized in Supplemental Table 3. The risk of death more than doubled (HR [95% CI], 2.176 [1.348-3.511]; $P = .001$) if 2 conventional parameters indicated dysfunction and nearly tripled (HR [95% CI], 2.890 [1.707-4.891]; $P < .001$) if 3 parameters indicated dysfunction compared with if only one parameter indicated dysfunction. To determine which 2 conventional parameters should be assessed in combination, we calculated the HRs of all 3 possible combinations. The combination of FAC and FWLS indicating RV dysfunction showed the highest HR compared to 0 parameters indicating dysfunction (HR [95% CI], 5.841 [2.107-16.190]; $P = .001$; Supplemental Table 4). However, based on the log-rank tests, there were no significant differences between the Kaplan-Meier curves of any combination of 2 parameters and between any combination and the subgroup where all 3 parameters indicated dysfunction (Figure 2). There were also no significant differences between the Kaplan-Meier curves when the subgroups were created by evaluating whether a combination of 2 conventional parameters indicated RV dysfunction irrespective of the third parameter's value (Supplemental Figure 1).

Reclassification in the Full Cohort

Five hundred eleven patients (68%) had normal RV function as assessed by RVEF. Although the same number of patients were identified with normal RV function using TAPSE, 21% of them had impaired RVEF. Using FAC, only 404 patients had seemingly intact RV function; however, 15% of them had RV dysfunction based on RVEF classification. Free-wall longitudinal strain classified 567 patients without dysfunction; in this case, 17% reclassification occurred (Figure 3).

Conversely, 239 patients (32%) showed RV dysfunction as assessed by RVEF. Tricuspid annular plane systolic excursion identified the exact number of patients with dysfunction, but 46% of them were misclassified. The FAC-based classification categorized 346 patients into the dysfunction group, and an astonishing 49% of them showed no dysfunction using RVEF. One hundred eighty-three patients were diagnosed with dysfunction using FWLS, which classification was altered in 23% of the cases using RVEF (Figure 3).

The outcomes of the reclassified and nonreclassified patients were also compared to better understand the clinical significance of RVEF-based classification (Figure 4). Patients with normal conventional parameters reclassified to RV dysfunction had a more than 4-fold higher

Table 1 Demographic and clinical characteristics

	Overall (*n* = 750)	Alive (*n* = 638)	Dead (*n* = 112)	*P*
Baseline demographic characteristics				
Age, years	59.4 ± 17.4	58.1 ± 17.3	66.7 ± 15.6	**<.001**
Gender, male	506 (67.5)	432 (67.7)	74 (66.1)	.733
Height, m	1.70 ± 0.10	1.71 ± 0.10	1.70 ± 0.10	.316
Weight, kg	74.1 ± 15.2	74.2 ± 15.0	73.4 ± 16.2	.605
Body surface area, m^2	1.86 ± 0.23	1.86 ± 0.22	1.84 ± 0.24	.447
Body mass index, kg/m^2	25.4 ± 4.1	25.4 ± 4.0	25.4 ± 4.4	.936
Systolic blood pressure, mm Hg	123.9 ± 17.9	124.3 ± 17.2	121.5 ± 21.7	.186
Diastolic blood pressure, mm Hg	74.4 ± 12.5	74.5 ± 12.4	73.8 ± 12.8	.617
Heart rate, bpm	72.2 ± 15.9	71.5 ± 15.6	76.3 ± 17.2	**.025**
Risk factors and medical history:				
History of smoking, n (%)	204 (27.2)	173 (27.1)	31 (27.7)	.902
Diabetes, n (%)	149 (19.9)	113 (17.7)	36 (32.1)	**<.001**
Dyslipidemia, n (%)	343 (45.7)	293 (45.9)	50 (44.6)	.802
Hypertension, n (%)	450 (60.0)	377 (59.1)	73 (65.2)	.225
ICD, n (%)	76 (10.1)	53 (8.3)	23 (20.5)	**<.001**
Coronary artery disease:, n (%)	200 (26.7)	159 (24.9)	41 (36.6)	**.010**
Myocardial infarction, n (%)	159 (21.2)	131 (20.5)	28 (25.0)	.286
PCI, n (%)	175 (23.3)	143 (22.4)	32 (28.6)	.155
CABG, n (%)	26 (3.5)	17 (2.7)	9 (8.0)	**.004**
2D echocardiographic parameters:				
RVSP, mm Hg	36.0 ± 17.1	34.0 ± 15.6	47.4 ± 20.9	**<.001**
TAPSE, mm	19.8 ± 5.9	20.3 ± 5.9	16.6 ± 5.0	**<.001**
RV EDAi, cm^2/m^2	14.4 ± 4.4	14.1 ± 4.2	15.6 ± 5.4	**.002**
RV ESAi, cm^2/m^2	9.4 ± 3.9	9.1 ± 3.5	11.3 ± 4.9	**<.001**
FAC, %	35.4 ± 10.1	36.4 ± 9.7	29.4 ± 10.4	**<.001**
RV SLS, %	−13.8 ± 5.5	−14.3 ± 5.4	−11.2 ± 5.7	**.001**
RV FWLS, %	−24.5 ± 6.7	−25.1 ± 6.5	−20.5 ± 6.3	**.001**
3D echocardiographic parameters:				
LV EDVi, mL/m^2	82.5 ± 31.8	80.3 ± 28.6	94.2 ± 43.9	**<.001**
LV ESVi, mL/m^2	43.7 ± 29.9	40.9 ± 26.2	59.3 ± 42.2	**<.001**
LV SVi, mL/m^2	38.7 ± 13.1	39.4 ± 13.3	34.9 ± 10.8	**<.001**
LV EF, %	50.2 ± 14.8	51.5 ± 14.1	42.5 ± 16.4	**<.001**
RV EDVi, mL/m^2	80.1 ± 29.7	78.4 ± 28.7	89.4 ± 33.5	**<.001**
RV ESVi, mL/m^2	43.7 ± 22.6	41.5 ± 20.6	55.9 ± 28.4	**<.001**
RV SVi, mL/m^2	36.3 ± 11.6	36.8 ± 11.7	33.5 ± 10.2	**.006**
RVEF, %	47.1 ± 9.4	48.3 ± 8.6	40.0 ± 10.5	**<.001**

Continuous variables are presented as means ± SD, and categorical variables are reported as frequencies (%).
Boldface type denotes statistical significance.
CABG, Coronary artery bypass grafting; *EDAi*, end-diastolic area index; *ESAi*, end-systolic area index; *PCI*, percutaneous coronary intervention; *SLS*, RV septal longitudinal strain.

risk of death compared to the nonreclassified patients (TAPSE HR [95% CI], 4.395 [2.127-9.085]; $P < .001$; FAC HR [95% CI], 4.186 [1.476-11.880]; $P < .001$; FWLS HR [95% CI], 4.221 [2.115-8.426]; $P < .001$). Conversely, patients with abnormal conventional parameters reclassified to normal RV function had a much lower mortality risk compared to the nonreclassified patients (TAPSE HR [95% CI], 0.326 [0.199-0.532]; $P < .001$; FAC HR [95% CI], 0.308 [0.197-0.480]; $P < .001$; FWLS HR [95% CI], 0.195 [0.102-0.373]; $P = .002$). Importantly, however, there was an added mortality risk in those subgroups where RVEF was normal but TAPSE or FAC was abnormal compared to those subgroups where both RVEF and TAPSE or FAC were normal (TAPSE HR [95% CI], 2.111 [1.041-4.280]; $P = .014$; FAC HR [95% CI], 2.237 [1.142-4.384]; $P = .010$).

Reclassification According to Subgroups

The following subgroups were defined: aortic valve disease ($n = 120$, 16%), mitral valve disease ($n = 108$, 14%), heart transplant (HTX) recipients ($n = 91$, 12%), nonischemic dilated cardiomyopathy (DCM; $n = 88$, 12%), ischemic cardiomyopathy ($n = 76$, 10%), acute coronary

Table 2 Factors associated with all-cause mortality using univariable Cox regression

	Univariable Cox regression	
	HR [95% CI]	*P*
Baseline demographic characteristics:		
Age	1.040 [1.026-1.054]	**<.001**
Gender, male	0.861 [0.582-1.275]	.455
Height	0.235 [0.035-1.562]	.134
Weight	0.996 [0.983-1.008]	.495
Body surface area	0.645 [0.276-1.508]	.311
Body mass index	1.001 [0.955-1.050]	.961
Systolic blood pressure	0.993 [0.980-1.006]	.280
Diastolic blood pressure	0.992 [0.974-1.010]	.387
Heart rate	1.015 [1.001-1.029]	**.037**
Risk factors and medical history:		
History of smoking	1.087 [0.718-1.647]	.693
Diabetes	2.001 [1.343-2.982]	**<.001**
Dyslipidaemia	0.929 [0.639-1.350]	.699
Hypertension	1.273 [0.862-1.879]	.225
ICD	2.676 [1.688-4.242]	**<.001**
Coronary artery disease:	1.705 [1.159-2.506]	**.007**
Myocardial infarction	1.264 [0.823-1.942]	.284
PCI	1.367 [0.907-2.061]	.135
CABG	3.018 [1.525-5.974]	**.002**
2D echocardiographic parameters:		
RVSP	1.027 [1.019-1.035]	**<.001**
TAPSE	0.911 [0.881-0.942]	**<.001**
RV EDAi	1.061 [1.025-1.099]	**<.001**
RV ESAi	1.100 [1.064-1.137]	**<.001**
FAC	0.940 [0.924-0.957]	**<.001**
RV SLS	1.105 [1.067-1.144]	**<.001**
RV FWLS	1.101 [1.071-1.133]	**<.001**
3D echocardiographic parameters:		
LV EDVi	1.011 [1.006-1.015]	**<.001**
LV ESVi	1.014 [1.009-1.018]	**<.001**
LV SVi	0.969 [0.952-0.987]	**<.001**
LV EF	0.965 [0.954-0.976]	**<.001**
RV EDVi	1.010 [1.005-1.015]	**<.001**
RV ESVi	1.018 [1.013-1.024]	**<.001**
RV SVi	0.972 [0.954-0.991]	**.005**
RVEF	0.928 [0.913-0.944]	**<.001**

Boldface type denotes statistical significance.
CABG, Coronary artery bypass grafting; *EDAi*, end-diastolic area index; *ESAi*, end-systolic area index; *PCI*, percutaneous coronary intervention; *SLS*, RV septal longitudinal strain.

syndrome (ACS; $n = 82$, 11%), other cardiomyopathy ($n = 31$, 4%), and other subgroup with various cardiac diseases ($n = 154$, 21%). The baseline clinical and echocardiographic characteristics of different subgroups are summarized in Supplemental Table 5.

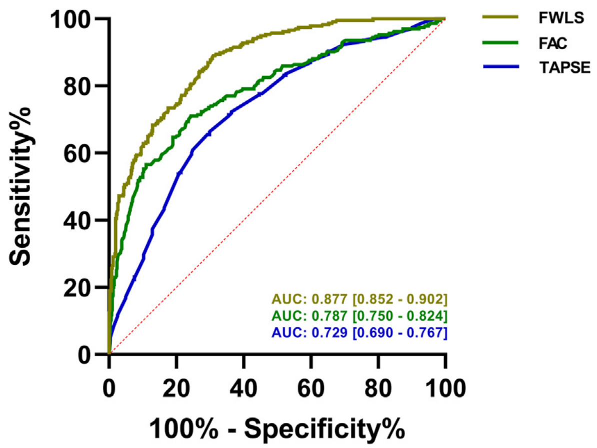


Figure 1 Receiver-operating characteristic curves of the conventional parameters for the discrimination of RV systolic dysfunction (RVEF <45%) with corresponding AUC values.

Regarding the subgroups' classification based on TAPSE, the highest rate of reclassification occurred in the case of HTX (71%), followed by ischemic cardiomyopathy (32%), nonischemic DCM (31%), aortic valve disease (25%), ACS (21%), and mitral valve disease subgroups (17%) (Supplemental Figure 2).

When FAC was used to assess RV function, patients with mitral valve disease were reclassified in 51%, HTX patients in 40%, nonischemic DCM in 30%, ischemic cardiomyopathy in 28%, aortic valve disease in 25%, and ACS in 17% (Supplemental Figure 3).

The assessment based on FWLS exhibited similar or lower rates of reclassification compared with the other conventional functional metrics: 28% of patients were reclassified in the ischemic cardiomyopathy, 20% in the nonischemic DCM and aortic valve disease, 19% in the HTX, 17% in the ACS, and 13% in the mitral valve disease subgroup (Supplemental Figure 4).

DISCUSSION

To the best of our knowledge, this study is the first to investigate the discordance between TAPSE, FAC, FWLS, and 3DE-derived RVEF in the detection of RV systolic dysfunction in a large cohort of patients with a wide variety of cardiac conditions. The main findings of our study can be summarized as follows: (1) RV dysfunction assessed based on the guideline-recommended cutoff values of TAPSE, FAC, and FWLS is only modestly concordant with the results of RVEF-based assessment, (2) RVEF-based reclassification is associated with a different clinical outcome, (3) reclassification rates vary depending on the parameter and the underlying pathology, (4) RV dysfunction indicated by FWLS shows the best agreement with RV dysfunction diagnosed based on RVEF, (5) combining impaired conventional parameters showed that outcomes are the worst if at least 2 parameters are impaired and gradually better if only one or none of them, and thus, (6) for the assessment of RV systolic function, a multiparametric approach is needed with the measurement of at least 2 conventional parameters when 3DE evaluation is not available.

Conventional echocardiographic parameters have long been utilized as reliable indicators of RV systolic function. These parameters, while widely used, only offer a partial representation of the complex functional characteristics of the RV, potentially limiting their ability to

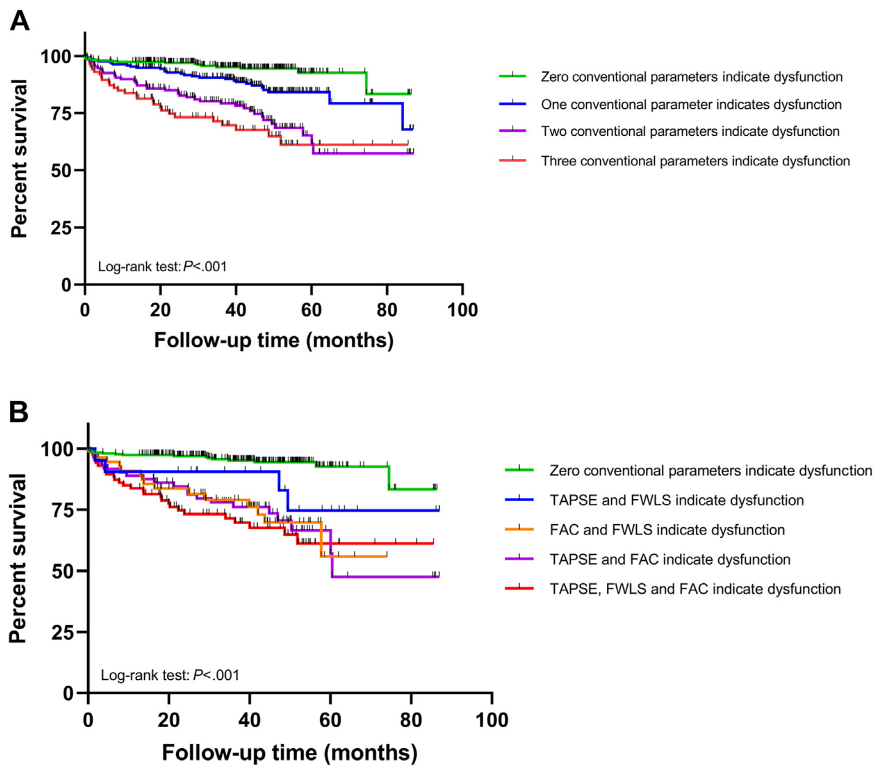


Figure 2 Survival analysis of patients divided into subgroups based on the number of conventional parameters indicating RV dysfunction **(A)** and based on the 2-parameter combinations of conventional parameters indicating RV dysfunction **(B).** The survival of patients is visualized via Kaplan-Meier curves with the *P* value of the overall log-rank test.

fully capture the spectrum of RV dysfunction and predict associated adverse clinical outcomes.

The conventional parameters are particularly vulnerable to inaccuracies in assessing RV systolic function, primarily due to their one- or two-dimensional nature, which fails to account for the intricate 3D geometry and contractile patterns of the RV.[3,4] Consequently, their sensitivity and specificity in identifying subtle alterations in RV function are compromised, as our results suggest. We have demonstrated that the degree of reclassification of RV systolic dysfunction is high (reaching 49% for FAC and 46% for TAPSE in the overall cohort) and depends on the parameter used and the underlying pathology. This reflects the fact that RV contraction patterns vary significantly according to specific pathophysiological conditions and different components of RV contractility may be affected by variable degrees.[9,10] According to our results, patients post-HTX were most frequently mislabeled as having an RV dysfunction based on conventional assessment using any parameters. The loss of pericardial constraint and the associated immediate decrease in RV longitudinal shortening compensated by increased radial shortening (the "bellows effect") are widely known consequences of the surgical opening of the pericardial sack that explains these findings.[11] Most likely due to the altered RV myofiber architecture and the ventricular interdependence, patients with different degrees of LV systolic dysfunction present with different contraction patterns that will be reflected in the reclassification rates of specific subgroups, for example, patients with different cardiomyopathies.[9] Free-wall longitudinal strain provided a more accurate classification of RV function and showed the closest association with RVEF compared to TAPSE or FAC.

In recent years, the advent of 3DE has significantly enhanced our understanding of cardiac anatomy and function. The 3DE technique allows for accurate volumetric assessment of the RV, providing a more comprehensive evaluation of its contractile performance. Reference values of RV volumes and EF are available to differentiate normal from abnormal RV.[12,13] Moreover, since it takes into account both the longitudinal and the radial component of the endocardial motion, and includes the RV outflow tract contribution, RVEF derived from the volumetric data offers a more comprehensive quantification of RV systolic function compared to traditional 2D parameters and shows excellent agreement with RVEF obtained with cardiac magnetic resonance.[6,14]

The independent prognostic value of 3DE-derived RVEF has been extensively demonstrated in various patient populations and is in agreement with our findings.[14-18] A recent meta-analysis has confirmed that RV dysfunction is robustly associated with all-cause mortality and adverse cardiopulmonary outcomes in patients with various cardiopulmonary diseases and demonstrated its superior prognostic importance compared to conventional echocardiographic parameters of RV function.[8] Thus, a 1 SD reduction in 3DE-derived RVEF showed a significantly stronger correlation with adverse events compared with a comparable change in TAPSE, FAC, or FWLS.

Nevertheless, 3DE-based assessment of the RV size and systolic function is not widely used in clinical practice yet.[19-21] Several factors may limit its routine implementation, such as dependence on the acoustic window, the need for training and expertise, and the need for 3DE probe and analysis software.[4] Using a multiparametric approach including qualitative and different conventional

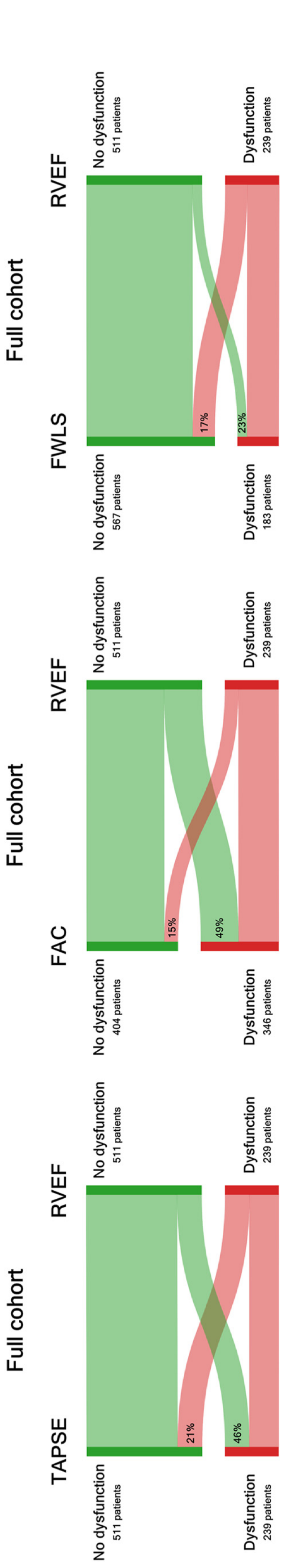


Figure 3 Disagreement in the classification of RV systolic function between conventional parameters and 3DE-derived RVEF. To visualize the rate of reclassification occurring in the full cohort by RVEF-based assessment, Sankey diagrams were constructed. *Green flows* represent patients without RV dysfunction, and *red flows* represent patients with RV dysfunction by RVEF.

quantitative metrics of the RV systolic function in centers not experienced in the 3DE-derived assessment of the RV size and function is another strategy being advocated by many experts;[21] however, there is no clear guidance on how these results from different RV parameters should be incorporated in the final definition of RV function and in clinical decision-making. In our manuscript, we provide evidence that RV systolic dysfunction diagnosed by 2 or more conventional echocardiographic parameters is associated with a worse prognosis compared with patients when only one parameter is abnormal. This can aid in the risk stratification of patients when 3DE assessment is unavailable or unfeasible. Additionally, we identify patients' subgroups with the highest reclassification rate of RV systolic function when assessed by specific conventional echocardiographic parameters. This can help select the most appropriate conventional metric(s) depending on the underlying cardiac pathology in line with precision medicine principles. Of note, patients with normal RVEF but abnormal TAPSE or FAC experienced worse outcomes than those with normal RVEF and also normal TAPSE or FAC, respectively. This phenomenon again highlights that subclinical changes in the RV contraction pattern might have added clinical value in the face of a maintained RVEF.

Some of the above issues could be resolved by future research and technological advancements. Guidance of 3DE acquisition, improved automation of 3D model reconstruction and contraction pattern assessment, artificial intelligence–based assessment of conventional metrics, or even the prediction of 3DE-derived RVEF from 2D echocardiography views may facilitate a quicker and more precise assessment of RV function.[22]

LIMITATIONS

Our study has several limitations that have to be acknowledged. First, an inherent limitation of our study is its retrospective design and the application of specific inclusion criteria (i.e., the availability of good-quality 3DE recordings) that may have introduced selection bias. However, the population analyzed in our study accurately represents the patient population seen in a tertiary care center, and we also included long-term outcome data to verify the clinical importance of our findings. Second, RVEF does not represent the gold standard for RV systolic function assessment. However, it is debatable whether there is a true gold standard parameter of RV function except for those obtained from invasively derived pressure-volume loops that cannot be used in population studies.[23] Theoretically, contractility (the intrinsic ability of the myocardium to shorten, independent of loading conditions) should be the target measure of all functional evaluations, yet conventional parameters, including RVEF, reflect ventriculo-arterial coupling rather than contractility.[24] The 3DE software packages used in our study are clinically well validated and have shown good concordance with the RVEF obtained by cardiac magnetic resonance imaging.[6,14] Nevertheless, we have to note that 3DE-based RV imaging is rarely utilized in clinical practice mainly due to the challenges of acquisition and the lack of postprocessing expertise, resulting in suboptimal success rates (81%-98% in experienced centers, but down to about 50% worldwide[8,25]). Third, the −20% cutoff for FWLS in the current guideline recommendations was determined based on data measured using a software solution different from the one we used in the current study.[4] However, by looking at the previously published data of a healthy population measured using TomTec's 4D RV-Function 2, the

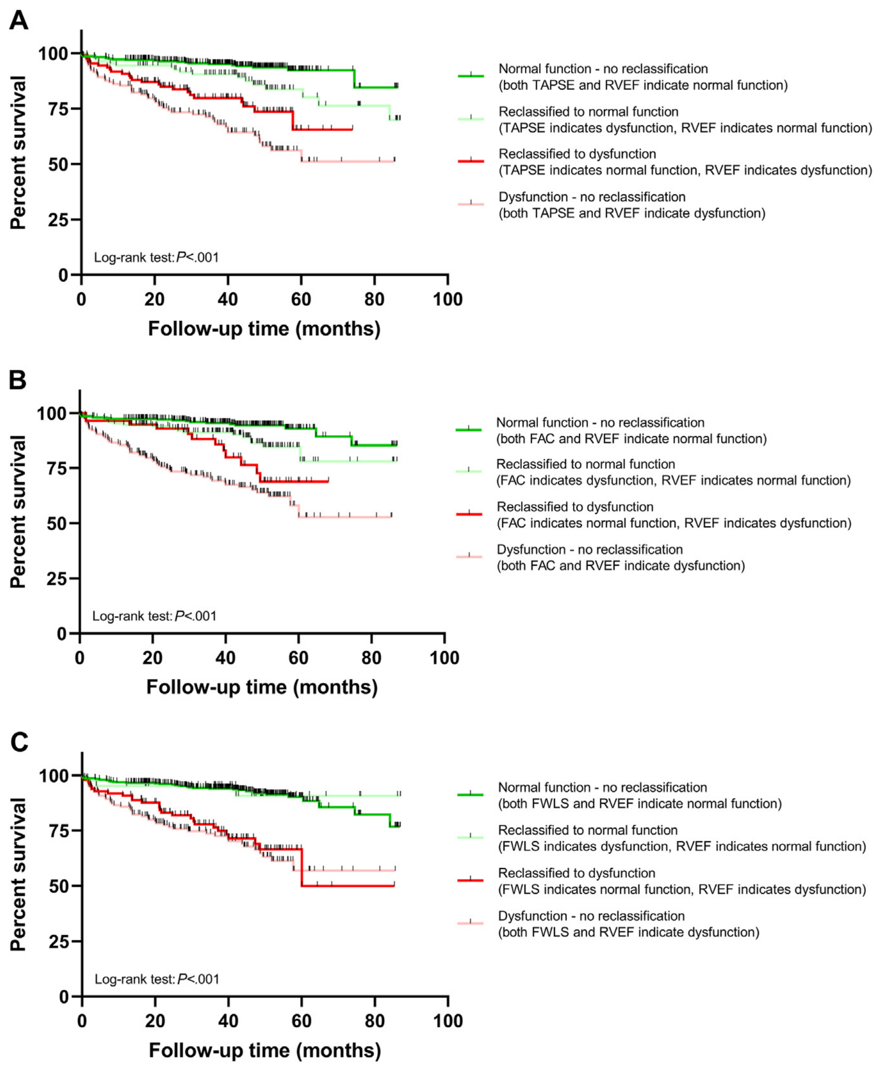


Figure 4 Survival analysis of patients divided into subgroups based on the combination of different parameters detecting RV systolic dysfunction. The survival of patients is visualized via Kaplan-Meier curves with the *P* value of the overall log-rank test. *Green and red colors* with the same opacity were used to indicate subgroups that were compared due to reclassification based on RVEF. (A) Patients are divided into subgroups based on the presence or absence of RV dysfunction determined by TAPSE, and with or without reclassification based on RVEF. (B) Patients are divided into subgroups based on the presence or absence of RV dysfunction determined by FAC, and with or without reclassification based on RVEF. (C) Patients are divided into subgroups based on the presence or absence of RV dysfunction determined by FWLS, and with or without reclassification based on RVEF.

−20% cutoff is still valid.[10] Fourth, due to the lack of cause-specific mortality data, we could not investigate the association between the 3DE-derived parameters and cardiac death. Last, the validity and generalizability of our results should be tested in prospective outcome studies in different races and clinical scenarios.

CONCLUSION

Guideline-recommended cutoff values of conventional echocardiographic parameters of RV systolic function are only modestly associated with RVEF-based assessment by 3DE, and the degree of RV function reclassification varies depending on the parameter used and the underlying pathology. Impaired values of FWLS show the closest association with the RVEF cutoff. A multiparametric approach for the assessment of RV systolic function is a preferable option when 3DE evaluation is not available. Presence of 2 or more conventional parameters indicating RV systolic dysfunction is associated with the worst outcomes.

REVIEW STATEMENT

Given his role as *JASE* Associate Editor, Luigi P. Badano, MD, PhD, and given her role as *JASE* Editor-in-Chief, Patricia A. Pellikka, MD, had no involvement in the peer review of this article and have no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Lawrence Rudski, MD.

CONFLICTS OF INTEREST

B.L., A.F., and A.K. report personal fees from Argus Cognitive, outside the submitted work. E.S. is an employee and shareholder of AstraZeneca and reports speaker honoraria from GE Healthcare and 123sonography, outside of the submitted work. All other authors report no competing interests that are directly or indirectly related to the work submitted for publication.

M.Tol. was supported by the EFOP-3.6.3-VEKOP-16-2017-00009 project and by the ÚNKP-23-3-II-SE-40 New National Excellence Program of the Ministry for Culture and Innovation from the source of the National Research, Development and Innovation Fund. Project no. RRF-2.3.1-21-2022-00003 has been implemented with the support provided by the European Union. TKP2021-EGA-23 has been implemented with the support provided by the Ministry of Innovation and Technology of Hungary from the National Research, Development and Innovation Fund, financed under the TKP2021-EGA funding scheme. This project was also supported by a grant from the National Research, Development and Innovation Office (NKFIH) of Hungary (FK 142573 to A.K.). A.K. was supported by the Janos Bolyai Research Scholarship of the Hungarian Academy of Sciences.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.echo.2024.04.005.

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