Association of Right Ventricular Functional Parameters With Adverse Cardiopulmonary Outcomes: A Meta-analysis

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Aims: We aimed to confirm that three-dimensional echocardiography–derived right ventricular ejection fraction (RVEF) is better associated with adverse cardiopulmonary outcomes than the conventional echocardiographic parameters.

Methods: We performed a meta-analysis of studies reporting the impact of unit change of RVEF, tricuspid annular plane systolic excursion (TAPSE), fractional area change (FAC), and free-wall longitudinal strain (FWLS) on clinical outcomes (all-cause mortality and/or adverse cardiopulmonary outcomes). Hazard ratios (HRs) were rescaled by the within-study SDs to represent standardized changes. Within each study, we calculated the ratio of HRs related to a 1 SD reduction in RVEF versus TAPSE, or FAC, or FWLS, to quantify the association of RVEF with adverse outcomes relative to the other metrics. These ratios of HRs were pooled using random-effects models.

Results: Ten independent studies were identified as suitable, including data on 1,928 patients with various cardiopulmonary conditions. Overall, a 1 SD reduction in RVEF was robustly associated with adverse outcomes (HR = 2.64 [95% CI, 2.18-3.20], $P < .001$; heterogeneity: $I^2 = 65\%$, $P = .002$). In studies reporting HRs for RVEF and TAPSE, or RVEF and FAC, or RVEF and FWLS in the same cohort, head-to-head comparison revealed that RVEF showed significantly stronger association with adverse outcomes per SD reduction versus the other 3 parameters (vs TAPSE, HR = 1.54 [95% CI, 1.04-2.28], $P = .031$; vs FAC, HR = 1.45 [95% CI, 1.15-1.81], $P = .001$; vs FWLS, HR = 1.44 [95% CI, 1.07-1.95], $P = .018$).

Conclusion: Reduction in three-dimensional echocardiography–derived RVEF shows stronger association with adverse clinical outcomes than conventional right ventricular functional indices; therefore, it might further refine the risk stratification of patients with cardiopulmonary diseases. (J Am Soc Echocardiogr 2023;36:624-33.)

Keywords: Right ventricular dysfunction, 3D echocardiography, Heart failure

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Abbreviations

2D = Two-dimensional

3D = Three-dimensional

CI = confidence interval

FAC = Fractional area change

FWLS = Free-wall longitudinal strain

GLS = Global longitudinal strain

HFpEF = Heart failure with preserved ejection fraction

HFrEF = Heart failure with reduced ejection fraction

HR = Hazard ratio

LV = Left ventricular

MOOSE = Meta-analysis of Observational Studies in Epidemiology

QUIPS = Quality in prognosis studies

RV = Right ventricular, ventricle

RVEF = Right ventricular ejection fraction

TAPSE = Tricuspid annular plane systolic excursion

INTRODUCTION

Assessment of right ventricular (RV) morphology and function is commonly included in comprehensive echocardiographic protocols of the clinical routine.[1] Right ventricular dysfunction is closely associated with symptom burden and excess mortality in patients with various cardiopulmonary conditions, warranting efforts to discover the condition in the early stages of the disease.[2]

The easily and routinely assessed parameters (e.g., tricuspid annular plane systolic excursion [TAPSE], fractional area change [FAC], and free-wall longitudinal strain [FWLS]) can only partially portray the complex functional characteristics of the right ventricle (RV); therefore, they may fail to capture the full spectrum of RV dysfunction and associated adverse clinical outcomes.[3]

Geometrically, the normal RV consists of a concave free-wall surface and an opposing convex interventricular septum resulting in a crescent-shaped short axis beyond the separated inflow and outflow parts. In that particular context, the M-mode and two-dimensional (2D) echocardiography–based measurements are rather simplistic approaches that do not account for such a complex three-dimensional (3D) shape, with the inherent risk of significant information loss. Moreover, from the functional aspect, recent data highlighted the importance of nonlongitudinal mechanical components, which are entirely neglected or just partially reflected by conventional measures.[4] Three-dimensional echocardiography–derived RV ejection fraction (RVEF) is a well-validated and reproducible parameter, which may overcome the shortcomings discussed above.[5] Despite the physiological and technical advantages of RVEF measurement, it remains to be elucidated whether RVEF shows more robust correlation with adverse clinical outcomes compared with conventional RV echocardiographic metrics.

Accordingly, we hypothesized that 3D echocardiography–derived RVEF shows better association with all-cause mortality and/or adverse cardiopulmonary outcomes than conventional echocardiographic parameters of RV systolic function.

RESEARCH DESIGN AND METHODS

Data Sources and Study Selection

This meta-analysis was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Guidelines.[6] The study protocol was preregistered on PROSPERO (registration number: CRD42018110771). Two collaborators (M.T. and A.K.) independently assessed articles from PubMed and EMBASE from inception until March 11, 2022, using a predefined search strategy with the following inclusion criteria (Figure 1 and Supplemental Table 1, available at www.onlinejase.com): (1) English-language studies published in peer-reviewed scientific journals; (2) studies reporting original investigations on human subjects; (3) adult age (>18 years) of all included participants; (4) studies with more than 20 subjects; (5) studies with 3D echocardiography performed and RVEF measured; (6) studies with all-cause mortality and/or adverse cardiopulmonary outcomes reported as hazard ratios (HRs; and 95% CIs) per unit change in 3D echocardiography–derived RVEF; and (7) studies that, at the same time, on the same cohort, reported at least 1 of the following RV functional parameters: TAPSE, FAC, or FWLS. A manual reference check of eligible full-text articles was performed to identify studies missed by our systematic search. Disagreement was resolved by consensus. When separate publications from the same research group on seemingly overlapping cohorts were identified, the study involving the higher number of subjects was included in our final analysis.

Data Extraction and Quality Assessment

Data were extracted on study design, baseline characteristics of the cohorts, echocardiographic parameters, feasibility and interobserver reproducibility of RVEF, and the predefined outcomes for all included studies by 2 collaborators (M.T. and A.K.). Study quality was ascertained using the Quality in Prognosis Studies (QUIPS) tool in consensus.[7]

Data Synthesis and Analysis

Hazard ratios and respective 95% CIs reporting the association between the unit change of the prespecified echocardiography-derived RV functional parameters (RVEF and TAPSE, or RVEF and FAC, or RVEF and FWLS) and clinical outcomes were extracted from eligible publications. We limited our inclusion to studies that allocated HRs for RVEF and TAPSE, or RVEF and FAC, or RVEF and FWLS to the same end point within each study, as per the inclusion criteria. The majority of studies reported HRs and 95% CIs relative to 1-unit increase in 3D RVEF (1% increase), TAPSE (1 mm increase), FAC (1% increase), and FWLS (1% increase in absolute value). Others reported these effect sizes per SD change.[8] To facilitate comparison of RVEF with TAPSE, FAC, and FWLS, all HRs and 95% CIs were rescaled by the within-study SD of the respective echocardiographic parameter to present a standardized change in the absolute value of each parameter (RVEF and TAPSE, or RVEF and FAC, or RVEF and FWLS) as described elsewhere.[9] Each SD reduction in the given echocardiographic parameter represents an increase in hazard, resulting in direct comparability of the predictive value of these parameters. Then the difference in logHRs (log of the ratio of HRs) of RVEF versus TAPSE, FAC, or FWLS was calculated within each study, and these estimates were pooled using a random-effects model (DerSimonian-Laird). This derived the pooled estimate and 95% CI, which was then transformed to be on the HR scale to quantify the association of RVEF with adverse clinical outcomes relative to the other metrics. A ratio of >1.00 denotes that a 1 SD reduction in RVEF is related to a greater hazard increment relative to a 1 SD reduction in the other metric. Therefore, these pooled estimates represent the overall difference in association of a 1 SD reduction in RVEF versus a 1 SD reduction in TAPSE, FAC, or FWLS, respectively. Forest plots were generated to visualize these differences. Statistical heterogeneity (referred to as heterogeneity) was assessed

HIGHLIGHTS

- RV dysfunction is associated with clinical outcomes in cardiopulmonary diseases.
- RVEF shows better correlation with adverse events compared with TAPSE, FAC, or FWLS.
- RVEF might be a universal biomarker that refines risk stratification.

using the Cochran Q homogeneity test and Higgins and Thompson I^2.[10] The I^2 heterogeneity was categorized as follows: 0% to 50%, low; 50% to 75%, moderate; >75%, high. As a post hoc analysis using mixed-effects meta-regression, we explored whether follow-up duration, differences in baseline disease of cohorts (primary diagnosis of pulmonary hypertension vs other cardiopulmonary conditions), or the type of end points (mortality only vs composite) explained the heterogeneity of the pooled estimates, yielding pseudo-R^2 values (which refers to the percentage of heterogeneity explained by the given variable). Additionally, we performed a subgroup analysis to compare the pooled estimates of studies reporting on cohorts with a primary diagnosis of pulmonary hypertension versus those that included patients with other cardiopulmonary conditions.

All statistical analyses were performed in Stata 17.0 (StataCorp LLC, College Station, TX). A 2-tailed $P < .05$ was considered statistically significant.

Sensitivity Analyses

Funnel plots were constructed to visually inspect the small-study effect (corresponding to publication bias) according to each echocardiographic parameter and related clinical outcomes. The nonparametric Begg's rank correlation test was used to quantify the association between the effect sizes and measures of precision (SEs). Nonparametric trim-and-fill analysis as per Duval and Tweedie was performed to correct for the small-study effect using the R0 estimator.[11] We used the DerSimonian-Laird random-effects method for both the iteration and pooling steps during the trim-and-fill analyses.

RESULTS

Study Selection and Characteristics

A total of 189 articles were subject to full-text review. According to the predefined inclusion and exclusion criteria, 13 studies were found suitable. In 3 instances (including 3-3 studies), there was an apparent overlap between the patient cohorts[8,12-16]; therefore, studies with a higher number of participants were included.[12,14,16] Overall,

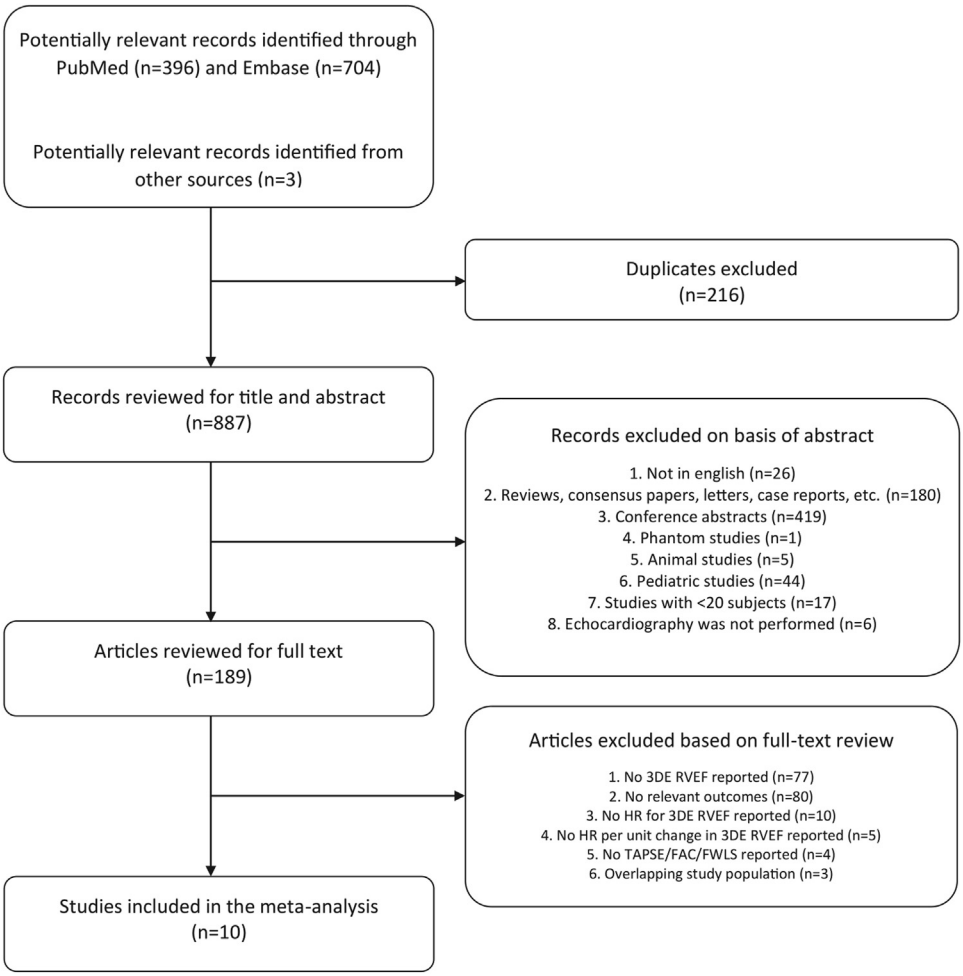

Figure 1 Study selection flowchart. *3DE*, 3D echocardiography.

Table 1 Study designs and clinical end points

Study	Sample size, *n*	Design	Population	Follow-up duration, months	End point	Events, *n* (%)
Murata (2016)	86	Retrospective	PAH	14.1	Cardiac events (death, hosp, intervention including PEA or BPA)	19 (22.1)
Moceri (2017)	104	Prospective	PH	6.7	Cardiopulmonary death	16 (15.4)
Surkova (2019)	394	Retrospective	Various cardiac diseases	44.4	All-cause mortality	56 (14.2)
Zhang (2021)	128	Prospective	COVID-19	3	All-cause mortality	18 (14.1)
Vîjiiac (2021)	50	Prospective	DCM	16	Cardiac death, nonfatal cardiac arrest, acute HF hosp	29 (53.7)
Li (2021)	203	Retrospective	PH	20.9	PH-related hosp; intervention or surgery including PEA or BPA; death	87 (42.9)
Meng (2021)	81	Prospective	HFpEF	17	HF death or HF rehosp	39 (48.1)
Tolvaj (2021)	174	Retrospective	Various cardiac diseases	24	All-cause mortality	24 (13.8)
Nabeshima (2021)	367	Retrospective	AS	26.7	Cardiac death, HF hosp, VT/VF, or nonfatal MI	57 (15.5)
Kitano (2022)	341	Retrospective	Various cardiac diseases	19.8	Cardiac death, VT, or HF hosp	49 (14.4)

AS, Aortic stenosis; *BPA*, balloon pulmonary angioplasty; *DCM*, dilated cardiomyopathy; *HF*, heart failure; *hosp*, hospitalization; *MI*, myocardial infarction; *PAH*, pulmonary arterial hypertension; *PEA*, pulmonary endarterectomy; *PH*, pulmonary hypertension; *VF*, ventricular fibrillation; *VT*, ventricular tachycardia.

10[12,14,16-23] independent studies were included in the final quantitative analysis (Figure 1), which reported the impact of unit change of RVEF and TAPSE (n = 8),[12,15,17,19-23] or FAC (n = 7),[12,18-23] or FWLS (n = 7)[16,18-23] on clinical outcomes (all-cause mortality and/or cardiopulmonary adverse events) as HRs. Four studies were prospective, while 6 were retrospective. Only 3 studies reported associations with all-cause mortality,[12,21,23] and the others reported composite cardiopulmonary end points (Table 1). We assessed the risk of bias within the studies using the QUIPS tool (Supplemental Figure 1, available at www.onlinejase.com).

Echocardiographic Measurements

All study subjects in the selected 10 studies underwent standard echocardiographic examination by experienced sonographers using commercially available ultrasound scanners (Supplemental Table 2, available at www.onlinejase.com). All of the measurements were performed and reported in the published articles by the corresponding study investigators. Right ventricular ejection fraction was measured by a single commercially available software in all the cases (TomTec 4D RV-Function, TomTec Imaging GmbH; reported ver. 2.0 or newer, standalone or embedded into another vendor's platform). In the vast majority of cases, an RV-focused apical window was used to acquire the full-volume 3D echocardiographic data set using multibeat reconstruction, which was finally utilized to measure RVEF. The initial semiautomated 3D contouring was further corrected manually by the investigators. Feasibility of RVEF measurement ranged from 81% to 98% across the 10 studies, which also reported good interobserver agreement (Supplemental Table 2, available at www.onlinejase.com). Tricuspid annular plane systolic excursion was measured using an M-mode recording, while FAC was assessed by contouring the end-diastolic and end-systolic RV endocardial surfaces in accordance with current guidelines.[1] Two-dimensional FWLS was measured using commercially available software packages from 2 vendors (Supplemental Tables 2 and 3, available at www.onlinejase.com).

Patient Characteristics

The 10 studies comprised data on 1,928 patients. Clinical characteristics and definitions of composite end points are shown in Tables 1 and 2. The mean (±SD) age of the patient population was 63 ± 15 years, 46% were female, and the follow-up duration ranged from 3 to 44 months. Three studies included patients with pulmonary hypertension exclusively,[14,16,20] 1 included patients with COVID-19 only,[23] 1 included patients with dilated cardiomyopathy only,[22] 1 included patients with aortic stenosis only,[18] 1 included heart failure patients with preserved left ventricular (LV) ejection fraction (HFpEF) only,[19] and the remaining 3 studies included populations with a mixture of cardiovascular diseases.[12,17,21]

Outcomes

Table 1 contains the definitions of end points assessed in each included study. Among the 1,928 patients, 394 (20.4%) reached the end point of all-cause mortality and/or adverse cardiopulmonary events.

In the 10 studies, a 1 SD reduction in RVEF was associated with a 2.64-fold (95% CI, 2.18-3.20, $P < .001$) increase in the risk of all-cause mortality and/or adverse cardiopulmonary events (Figure 2). The moderate heterogeneity (I^2 = 65%, P = .002) found across studies was not explained by differences between follow-up duration (pseudo-R^2 = 2%, P = .062), end point definitions (pseudo-R^2 = 0%, P = .806), or primary diagnosis of pulmonary hypertension (pseudo-R^2 = 0%, P = .524). Regarding end point definitions, 3 studies comprising 696 patients reported on all-cause mortality. Accordingly, a 1 SD reduction in RVEF was associated with a 2.63 times (95% CI, 1.60-4.30, $P < .001$) higher risk of death from any cause (Supplemental Figure 2, available at www.onlinejase.com).

Table 2 Demographic and clinical characteristics of the study populations

Study	Age, years	Female, *n* (%)	BMI, kg/m^2	BSA, m^2	HR, bpm	SBP, mm Hg	DBP, mm Hg	DM, *n* (%)	HTN, *n* (%)	DLP, *n* (%)	CAD, *n* (%)	CKD, *n* (%)
Murata (2016)	50 ± 17	63 (72)	NA	1.6 ± 0.2	72 ± 14	111 ± 17	64 ± 13	NA	NA	NA	NA	NA
Moceri (2017)	66 (62-69)	58 (56)	NA	1.72 ± 0.2	NA	NA	NA	NA	NA	NA	NA	NA
Surkova (2019)	57 (42-69)	136 (35)	24.5 (22.1-26.8)	1.81 (1.67-1.95)	68 (59-77)	120 (110-130)	70 (70-80)	51 (12.9)	190 (48.2)	143 (36.3)	119 (30.2)	NA
Zhang (2021)	61 ± 13	80 (50)	NA	1.67 ± 0.15	86 (80-99)	130 (120-140)	80 (73-88)	18 (14.1)	52 (40.6)	NA	NA	1 (0.8)
Vijiac (2021)	61 ± 14	16 (32)	NA	NA	79 ± 16	124 ± 13	75 ± 11	9 (18)	34 (68)	NA	0 (0)	NA
Li (2021)	49 ± 15	146 (72)	NA	1.7 ± 0.2	NA	NA	NA	NA	NA	NA	NA	NA
Meng (2021)	62 ± 12	18 (35)	25.5 ± 3.6	NA	72.4 ± 11.5	136.3 ± 22.6	83.0 ± 14.9	36 (44.4)	46 (56.8)	NA	NA	NA
Tolvaj (2021)	62 ± 14	48 (28)	NA	1.9 ± 0.2	NA	126.2 ± 19.7	74.7 ± 16.5	39 (22.5)	113 (65.3)	NA	38 (22)	NA
Nabeshima (2021)	77 ± 10	199 (54)	22.7 ± 3.9	1.52 ± 0.21	69.5 ± 12.6	147.5 ± 23.5	75.0 ± 13.5	115 (31)	295 (80)	NA	79 (22)	174 (47)
Kitano (2022)	68 (58-76)	115 (34)	NA	1.62 (1.50-1.75)	67 (59-76)	127 (112-145)	71 (63-79)	101 (30)	191 (56)	149 (44)	143 (42)	149 (44)

Data are presented as mean ± SD or median (interquartile range), unless otherwise indicated. *BMI*, Body mass index; *BSA*, body surface area; *CAD*, coronary artery disease; *CKD*, chronic kidney disease; *DBP*, diastolic blood pressure; *DLP*, dyslipidemia; *DM*, diabetes mellitus; *HR*, heart rate; *HTN*, systemic arterial hypertension; *SBP*, systolic blood pressure.

Furthermore, we conducted a subgroup analysis of studies reporting outcomes on patients with a primary diagnosis of pulmonary hypertension ($n = 3$ studies, overall 393 patients) versus those studies including patients with other cardiopulmonary conditions ($n = 7$ studies, overall 1,535 patients). We found that RVEF showed robust correlation with adverse outcomes in patients with (HR = 2.97 [95% CI, 2.12-4.14]) and without (HR = 2.57 [95% CI, 2.04-3.24]) pulmonary hypertension (Supplemental Figure 3, available at www.onlinejase.com). Given the vast overlap of CIs, the interaction between these 2 subgroups was nonsignificant ($P = .49$), suggesting that RVEF correlates with clinical outcomes regardless of whether pulmonary hypertension is the primary cause of RV dysfunction.

The funnel plot (Supplemental Figure 4, available at www.onlinejase.com) and Begg's test for small-study effects ($z = -1.43$, $P = .15$) showed that risk of publication bias was low. Accordingly, the trim-and-fill analysis (Supplemental Figure 5, available at www.onlinejase.com) showed that even if significant 1-tailed publication bias occurred that favored the publication of highly positive studies (suggesting that reduction in RVEF is strongly associated with adverse clinical outcomes), our pooled study estimate would not have been significantly altered (adjusted HR = 2.32 [95% CI, 1.86-2.90]).

In studies reporting HRs for RVEF and TAPSE simultaneously in the same cohort ($n = 8$; 1,358 patients), the SD reductions in RVEF (HR = 2.76 [95% CI, 2.16-3.54]) and TAPSE (HR = 1.81 [95% CI, 1.43-2.28]) were both significantly associated with adverse clinical outcomes (Supplemental Figure 6, available at www.onlinejase.com). However, the HR per SD change for RVEF as a correlate of outcomes was 1.54 (95% CI, 1.04-2.28, $P = .031$) times greater than that of TAPSE, with moderate heterogeneity ($I^2 = 74\%$, $P < .001$; Figure 3). The latter was not related to study differences in follow-up duration (pseudo-$R^2 = 17\%$, $P = .15$), end point definitions (pseudo-$R^2 = 0\%$, $P = .95$), or primary diagnosis of pulmonary hypertension (pseudo-$R^2 = 0\%$, $P = .68$). Begg's test for small-study effects ($z = 0.62$, $P = .54$) indicated no evidence of substantial 1-sided publication bias (Supplemental Figure 7, available at www.onlinejase.com).

In studies reporting HRs for RVEF and FAC in the same cohort ($n = 7$; 1,280 patients), we found that a 1 SD reduction in RVEF (HR = 2.68 [95% CI, 2.09-3.42]) and FAC (HR = 1.71 [95% CI, 1.44-2.02]), respectively, was associated with adverse outcomes in patients with various diseases (Supplemental Figure 8, available at www.onlinejase.com). The above HR per SD reduction in RVEF translates into 1.45 (95% CI, 1.15-1.81, $P = .001$) times greater risk of adverse outcomes compared to that of FAC (Figure 4). In this analysis, heterogeneity was low ($I^2 = 39\%$, $P = .13$), to which differences in follow-up duration (pseudo-$R^2 = 0\%$, $P = .39$), end point definitions (pseudo-$R^2 = 0\%$, $P = .22$), and primary diagnosis of pulmonary hypertension (pseudo-$R^2 = 0\%$, $P = .89$) made no significant contribution. The presence of publication bias in this analysis was not supported by the visual inspection of the funnel plot (Supplemental Figure 9, available at www.onlinejase.com) and Begg's test ($z = 0.30$, $P = .76$).

Finally, in studies reporting the association of unit change in RVEF and FWLS on clinical outcomes in the same cohort ($n = 7$; 1,089 patients), we found that a 1 SD decrease in these parameters was significantly associated with adverse events (RVEF, HR = 2.76 [95% CI, 2.06-3.70]; FWLS, HR = 1.77 [95% CI, 1.42-2.21]; Supplemental Figure 10, available at www.onlinejase.com). However, the strength of effect for the HR per SD reduction for RVEF was 1.44 (95% CI, 1.07-1.95, $P = .018$) times higher than that of FWLS, suggesting a

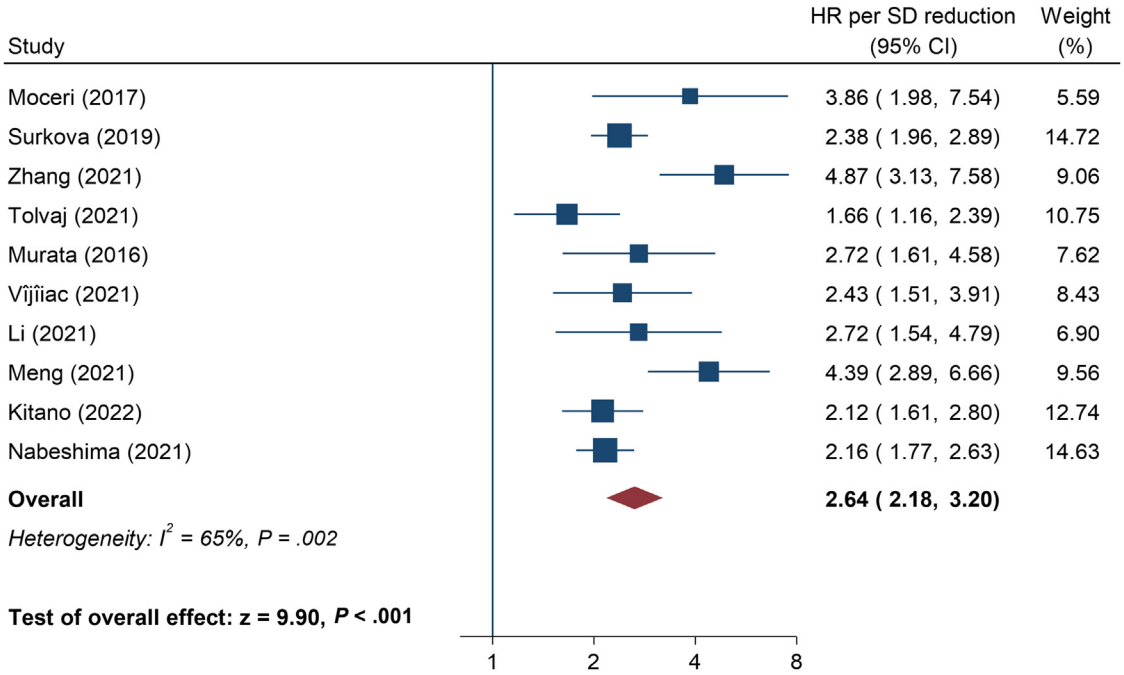

Figure 2 Three-dimensional echocardiography–derived RVEF and its association with all-cause mortality and/or composite adverse cardiopulmonary end points. The HRs are per 1 SD reduction in RVEF according to each study. Accordingly, an HR of >1.00 means that a 1 SD reduction in RVEF is associated with an increased risk of adverse events.

more robust association (Figure 5). None of the investigated factors (follow-up duration: pseudo-$R^2 = 0\%$, $P = .96$; end point differences: pseudo-$R^2 = 0\%$, $P = .18$; primary diagnosis of pulmonary hypertension: pseudo-$R^2 = 0\%$, $P = .60$) contributed significantly to the low level of heterogeneity ($I^2 = 47\%$, $P = .08$). No substantial small-study effect was present based on the funnel plot (Supplemental Figure 11, available at www.onlinejase.com) and Begg's test ($z = 0.30$, $P = .76$).

DISCUSSION

In this meta-analysis, we found that RV dysfunction is robustly associated with all-cause mortality and adverse cardiopulmonary outcomes in patients with various cardiopulmonary diseases. All 4 investigated echocardiographic parameters of RV systolic function were associated with these end points; however, a 1 SD reduction in 3D echocardiography–derived RVEF showed a significantly stronger correlation with adverse events compared with a comparable change in TAPSE, FAC, or FWLS (Graphical Abstract).

Clinical Significance of RV Systolic Dysfunction

Studies over the last decade have identified RV dysfunction as a correlate of symptom burden and a powerful predictor of adverse outcomes not only in right-sided heart diseases but also in conditions affecting the left ventricle primarily.[24] In fact, the prevalence of RV dysfunction in patients with HFrEF is 47%, being independently associated with excess mortality and heart failure admissions.[25] Furthermore, one-third of patients with HFpEF present with a significant RV dysfunction.[26] The presence of RV systolic dysfunction alongside the diagnosis of HFpEF carries a ~6 times higher risk of 2-year mortality compared with the absence of it.[26] Therefore, timely identification of RV dysfunction using sensitive and reliable functional parameters might enable a more sophisticated risk stratification in the clinical setting.

Role of Echocardiography in the Assessment of RV Function

According to 2 recent surveys, the most commonly used echocardiographic parameters to assess RV systolic function in the clinical routine is the M-mode TAPSE, followed by tissue Doppler imaging-derived S′ and FAC.[27,28] There is evidence that RV dysfunction is diagnosed in 37% of HFpEF patients by TAPSE, whereas FAC identifies a considerably lower fraction of cases (26%).[29] A meta-analysis also reported vast differences in the identification of RV dysfunction across parameters, with TAPSE suggesting RV dysfunction in 31% of HFpEF subjects, compared with 26% and 13% by S′ and FAC, respectively.[30] These considerable diagnostic dissimilarities between conventional echocardiography-derived indices of RV function might stem from the complex 3D anatomy and distinct contraction patterns of the RV.[13,14] Due to altered RV mechanics, for example, TAPSE can underestimate global function post–cardiac surgery and in patients with different degrees of LV systolic dysfunction,[13,31] while it may overestimate it in volume overload–induced RV remodeling.[3,32] Therefore, a unifying RV functional parameter that can circumvent such limitations would be ideal for quantifying RV dysfunction and associated clinical risk in various pathological conditions. While 2D speckle-tracking echocardiography might overcome many limitations of conventional parameters by being less dependent on the angle of insonation and RV loading conditions,[33] it still represents a single 2D tomographic plane. On the contrary, 3D echocardiography maps the entire endocardial surface of the RV independent of any assumption about its shape and function, providing an integrative parameter of RV systolic function—RVEF.[24]

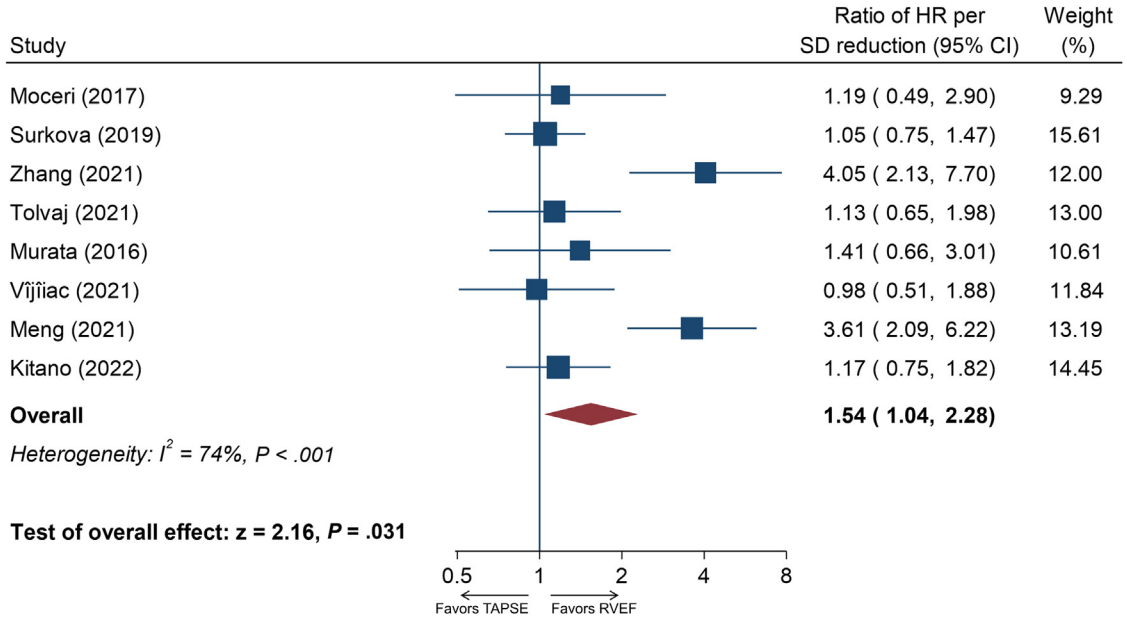

Figure 3 Three-dimensional echocardiography–derived RVEF versus TAPSE by their association with all-cause mortality and/or composite adverse cardiopulmonary end points. The ratios of HRs per 1 SD reduction in RVEF/TAPSE are depicted. Accordingly, an HR >1.00 means that a 1 SD reduction in RVEF is associated with a higher risk of adverse events compared with a 1 SD reduction in TAPSE.

Nonetheless, current literature has not elucidated whether 3D echocardiography–derived RVEF correlates stronger with adverse clinical outcomes compared with other indices of RV function.

Association of Different Parameters of RV Systolic Function With Adverse Clinical Outcomes

The present meta-analysis demonstrated that 3D echocardiography–derived RVEF showed a robust association with adverse outcomes. We estimated that a 1 SD reduction in RVEF conferred a ~2.6 times higher risk of all-cause mortality and/or adverse cardiopulmonary events in a broad spectrum of patients with various cardiopulmonary conditions. This association was unaffected by whether the population consisted of patients with a primary diagnosis of pulmonary hypertension. In fact, reduction in RVEF correlates with adverse clinical outcomes to a similar extent in patients with and without pulmonary hypertension. Therefore, our meta-analysis extends previous studies by showing that RV dysfunction forecasts adverse clinical events not only in patients with pulmonary hypertension[3,4] but also in those with heart failure, COVID-19, and aortic stenosis. Furthermore, our estimate was not affected by differences in follow-up durations and whether the studied end point included all-cause mortality only or other composite cardiopulmonary end points. Specifically, we found that a 1 SD reduction in RVEF is associated with ~2.6 times higher risk of death from any cause. Finally, we estimated that even if substantial publication bias occurred, our estimate would not significantly change.

As for the other parameters, we calculated that reduction in TAPSE, FAC, and FWLS also correlated with adverse clinical outcomes, respectively. In fact, a 1 SD reduction in each of these parameters was associated with a 1.71 to 1.81 times higher risk of unfavorable events. Therefore, RV dysfunction is associated with clinical outcomes irrespective of the echocardiographic parameter used. However, in a head-to-head comparison, we found that a 1 SD reduction in RVEF conferred a 1.44 to 1.54 times higher risk of adverse outcomes compared with a comparable reduction in TAPSE, FAC, and FWLS, respectively, in the very same patient populations. Consequently, 3D echocardiography–derived RVEF might identify a broader spectrum of high-risk patients with RV dysfunction, in contrast with the other parameters, rendering it a more valuable tool to risk-stratify patients with various cardiopulmonary conditions. This might translate into a timely identification of high-risk patients, also paving the way for future studies to develop effective countermeasures.

In the head-to-head comparisons, RVEF showed a better association with adverse clinical outcomes versus TAPSE, FAC, and FWLS, irrespective of whether the studied population included patients with pulmonary hypertension only or not. Therefore, RVEF might also overcome the limitations of these parameters in primary left-heart diseases. Furthermore, differences in end point definitions and follow-up durations had no significant impact on the superiority of RVEF's association with adverse outcomes. In a similar attempt to assess the pooled prognostic significance of different parameters of LV systolic function, a previous meta-analysis showed that LV global longitudinal strain (GLS) had a superior predictive value compared to LVEF.[9] Notably, in our present meta-analysis focusing on RV function, RVEF was shown to be better associated with adverse outcomes compared with FWLS. This important finding may be attributable to the fact that RV FWLS reflects only 1 mechanical component (longitudinal shortening) in a single 2D tomographic plane (unlike 3 planes for LV GLS assessment) and, therefore, may not be an adequate representation of the contraction pattern of the complex 3D structure of the RV, especially under different pathophysiological conditions.

Overall, the results of our current meta-analysis support the broader implementation of 3D echocardiography for the assessment of RV systolic function in patients with cardiopulmonary disorders—irrespective of the primary site of the disease. Of note, 3D image

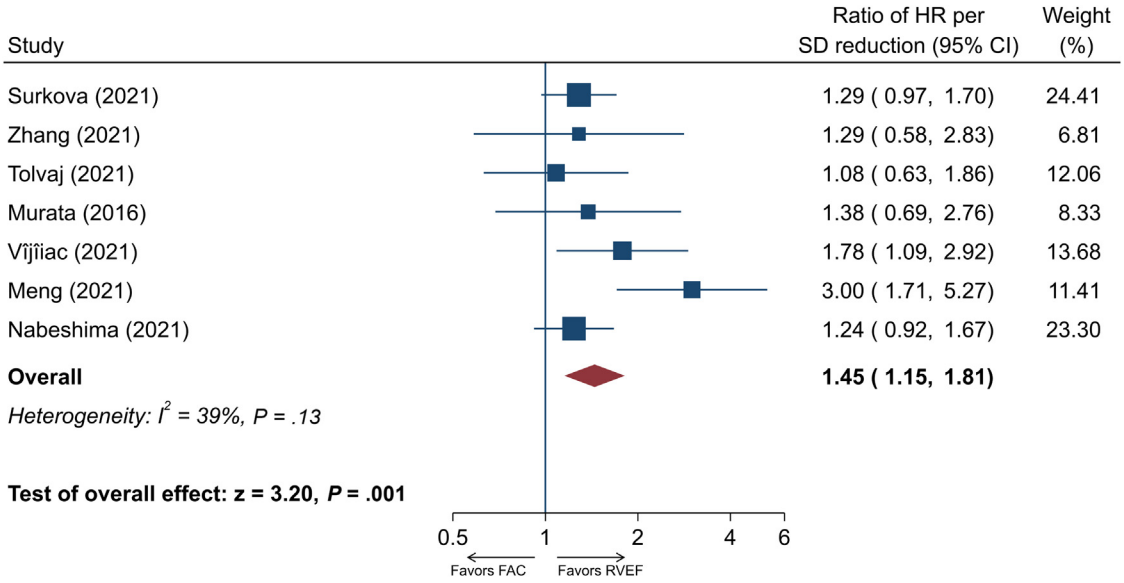

Figure 4 Three-dimensional echocardiography–derived RVEF versus FAC by their association with all-cause mortality and/or composite adverse cardiopulmonary end points. The ratios of HRs per 1 SD reduction in RVEF/FAC are shown. Accordingly, a ratio of HR >1.00 means that a 1 SD reduction in RVEF is associated with a higher risk of adverse events compared to a 1 SD reduction in FAC.

acquisition and postprocessing require an advanced hardware and software environment and have a learning curve. According to a worldwide survey, 50% of current ultrasound systems already have transthoracic 3D probes available, yet only 17% of the participants use it frequently to measure RVEF.[35] There is a common belief that the quantification of RVEF is a lengthy process with low success rates. However, it has been recently demonstrated that the use of contemporary automated 3D software solutions may even result in shorter analysis times compared with routine 2D evaluations.[36] Recently published articles (including those incorporated in the current analysis) reported a feasibility over 90% along with good reproducibility, which is in line with our own experience. As the seemingly most powerful index of RV function, the inclusion of RVEF in everyday clinical decision-making and risk stratification models seems justified by the current knowledge base. Moreover, the assessment of RVEF as a trigger for specific therapies may also lead to clinical benefits for patients in the future. However, these need to be tested in rigorous clinical trials.

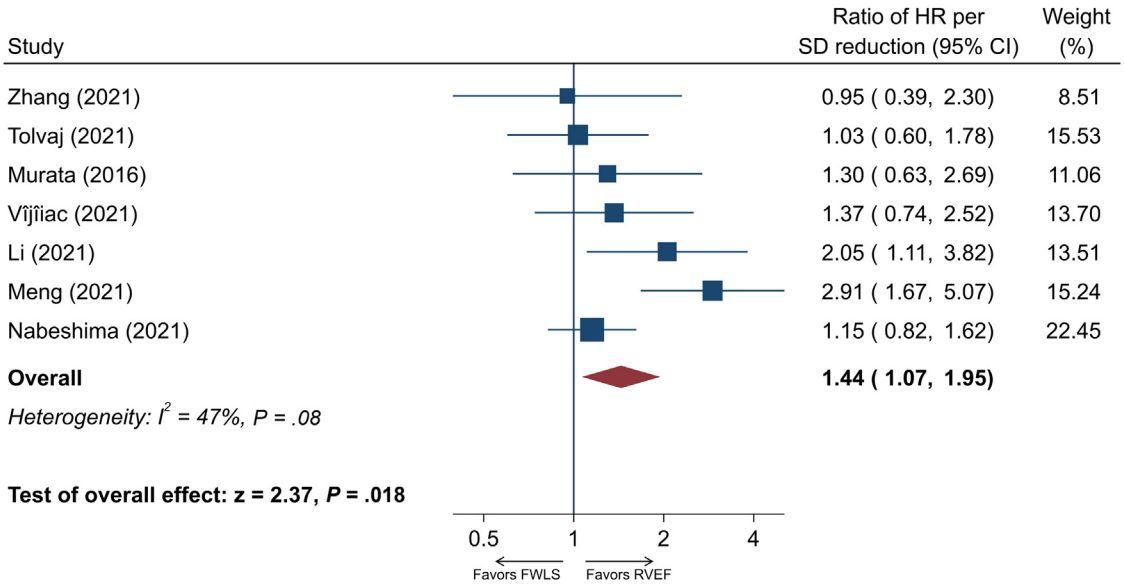

Figure 5 Three-dimensional echocardiography–derived RVEF versus FWLS by their association with all-cause mortality and/or composite adverse cardiopulmonary end points. The ratios of HRs per 1 SD reduction in RVEF/FWLS are depicted. Accordingly, an HR >1.00 means that a 1 SD reduction in RVEF is associated with a higher risk of adverse events compared to 1 SD reduction in FWLS.

Limitations

The validity of the present meta-analysis is subject to the quality of the reporting of the included studies, rendering our findings hypothesis generating only. First, the studies included in this meta-analysis were nonuniform in design and varied in the inclusion criteria, patients populations, echocardiographic equipment, technical aspects of 3D RV data acquisition, duration of follow-up, and definition of end points. Therefore, we opted for using a random-effects meta-analysis and performed a mixed-effects meta-regression to estimate the contribution of select factors (differences in patient populations, follow-up, and end point definitions) to the observed results. Second, not all 10 studies included in the current meta-analysis provided quantification of 3D echocardiography–derived RVEF and all 3 other RV parameters of interest at the same time, which led to a smaller number of studies included in each comparison (8 for RVEF vs TAPSE, 7 for RVEF vs FAC, and 7 for RVEF vs FWLS). Third, the majority of the included studies per se implied the result that RVEF is better associated with adverse outcomes. However, in our meta-analysis we were able to exactly quantify this added value against several routine measures resulting in higher-level evidence that supports the clinical use of RVEF. Lastly, as prespecified, due to a considerably lower amount of available and comparable data, tissue Doppler-derived tricuspid annular S′ velocity and RV GLS (either 2D or 3D) were not included in our analysis. While the former measures longitudinal shortening exclusively, the predictive value of 2D RV GLS has recently been shown to be inferior compared with FWLS in HFrEF.[37]

CONCLUSION

Reduction in RV systolic function is robustly associated with adverse clinical outcomes in patients with various cardiopulmonary conditions. Three-dimensional echocardiography–derived RVEF identifies a broader spectrum of patients at risk than other RV systolic functional parameters (TAPSE, FAC, or FWLS), regardless of whether the primary cause of RV dysfunction was related to pulmonary hypertension or not. Therefore, RVEF might be a universal marker of RV function, which might further refine the risk stratification of patients and inform clinical decision-making, potentially facilitating timely interventions.

DATA AVAILABILITY

Data will be made available on request.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.echo.2023.01.018.

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SUPPLEMENTARY DATA

Supplemental Table 1 Search syntax

(“3D”[All Fields] OR “3-D”[All Fields] OR “3-dimensional”[All Fields] OR “three-dimensional”[All Fields] OR “4D”[All Fields] OR “4-D”[All Fields] OR “4-dimensional”[All Fields] OR “four-dimensional”[All Fields]) AND (“Echocardiography”[MeSH Terms] OR echocardiograph*[All Fields] OR “echo”[All Fields] OR “ultrasound”[All Fields]) AND (“right ventricular”[All Fields] OR “RV”[All Fields] OR “right ventricle”[All Fields] OR “right heart”[All Fields]) AND (“ejection fraction”[All Fields] OR “EF”[All Fields] OR “RVEF”[All Fields] OR “3DRVEF”[All Fields] OR “failure”[All Fields] OR “dysfunction”[All Fields]) AND (“cardiac event”[All Fields] OR “cardiovascular event”[All Fields] OR “major cardiovascular events”[All Fields] OR “major adverse cardiovascular events”[All Fields] OR “MACE”[All Fields] OR “cardiac death”[All Fields] OR “cardiovascular death”[All Fields] OR “death”[All Fields] OR mortalit*[All Fields] OR “Mortality”[MeSH Terms] OR hazard ratio*[All Fields] OR “HR”[All Fields] OR “Cox”[All Fields] OR “Cox regression”[All Fields] OR “proportional hazards regression”[All Fields] OR “hospitalization”[All Fields] OR “Hospitalization”[MeSH Terms] OR prognos*[All Fields] OR “Prognosis”[MeSH Terms] OR surviv*[All Fields] OR “Survival Analysis”[MeSH Terms] OR predict*[All Fields])

Supplemental Table 2 Echocardiographic setup of the 10 eligible studies

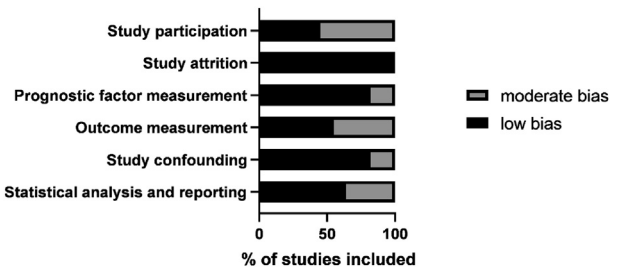
Study	Ultrasound system	Probe	3D volume rate, VPS	Single beat/ multibeat	RV-focused 3D-data set	Software	Software version	Manual correction	3D RVEF feasibility, %	3D RVEF interobserver reproducibility	FWLS software
Murata (2016)	GE Vivid E9	NA	NA	NA	NA	TomTec 4D RV-Function	NA	NA	87	CV: 1.5 ± 3.8 [95% CI, -6.3-9.2]	GE EchoPAC
Moceri (2017)	Philips iE33 or EPIQ 7	X5-1	17.7 (16.6–18.7)	2 beats	Yes	TomTec 4D RV-Function	2.0	Yes	92	ICC: 0.90 [95% CI, 0.77-0.96]	NA
Surkova (2019)	GE Vivid E9	4V-D	NA	4-6 beats	Yes	TomTec 4D RV-Function	2.0	Yes	85	ICC: 0.89	NA
Zhang (2021)	Philips EPIQ 7C	NA	NA	Single beat	Yes	3D Auto RV, Philips	NA	Yes	81	ICC: 0.91	TomTec CPA
Vijiiac (2021)	GE Vivid E9	4V-D	NA	6 beats	Yes	TomTec 4D RV-Function	NA	Yes	83	ICC: 0.90 [95% CI, 0.54-0.97]	GE EchoPAC
Li (2021)	Philips EPIQ 7C	X5-1	NA	Up to 6 beats	Yes	3D Auto RV, Philips	NA	Yes	89	CV: -0.02 ± 1.06 [95% CI, –2.10-2.06]	NA
Meng (2021)	Philips iE33	NA	20-35	4 beats	Yes	TomTec 4D RV-Function	2.0	Yes	87	ICC: 0.82	TomTec CPA
Tolvaj (2021)	Philips EPIQ/ GE Vivid E95	X5-1/4V-D or 4Vc-D	Minimum 25	Mixed single and multibeat	Yes	TomTec 4D RV-Function	2.0	Yes	90	NA	TomTec 4D RV-Function 2.0
Nabeshima (2021)	Philips iE33 or EPIQ 7G/GE Vivid7 or Vivid E95	X3-1 or X5-1/4V-D	NA	NA	Yes	TomTec 4D RV-Function	3.0	Yes	97	NA	TomTec AutoStrain RV
Kitano (2022)	Philips iE33 or EPIQ 7G/GE Vivid E95	X5-1/4V-D or 4Vc-D	23 (20-27)	Mixed single and multibeat	Yes	TomTec 4D RV-Function	3.0	Yes	98	ICC: 0.86	NA

CV, Coefficient of variability; *ICC*, intraclass correlation coefficient; *VPS*, volumes per second.

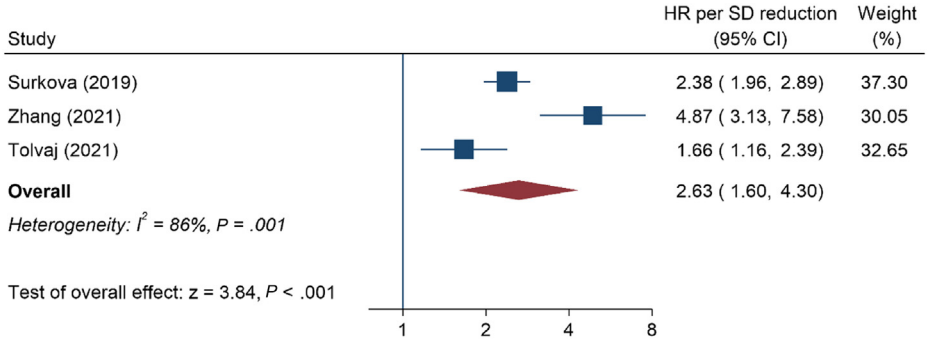
Supplemental Table 3 Comparison of the reported RV functional parameters

Study	3D RVEF	TAPSE	RV FAC	RV FWLS
Murata (2016)	43 ± 12	19 ± 4	31 ± 11	−19.7 ± 6.4
Moceri (2017)	35.6 ± 9.7	20.4 ± 5.2	NA	NA
Surkova (2019)	48 (41-52)	20 (16-24)	40 (32-45)	NA
Zhang (2021)	48.5 ± 5.8	22.9 ± 3.8	47.4 ± 5.7	−22.9 ± 4.8
Vijiiac (2021)	42 ± 10	18 ± 5	33 ± 12	−14.8 ± 8.3
Li (2021)	37.5 ± 9.1	15.5 ± 5.2	28.4 ± 8.8	−18.6 ± 5.5
Meng (2021)	45.6 ± 4.7	20.0 ± 3.0	41.5 ± 4.5	−20.5 ± 3.5
Tolvaj (2021)	46.9 ± 9	20.2 ± 6.6	41.1 ± 8.7	23.6 ± 7
Nabeshima (2021)	48.0 (43.7-52.7)	NA	40.1 (36.1-44.8)	24.6 (20.7–27.8)
Kitano (2022)	48 (40-54)	16.7 (13-20.6)	NA	NA

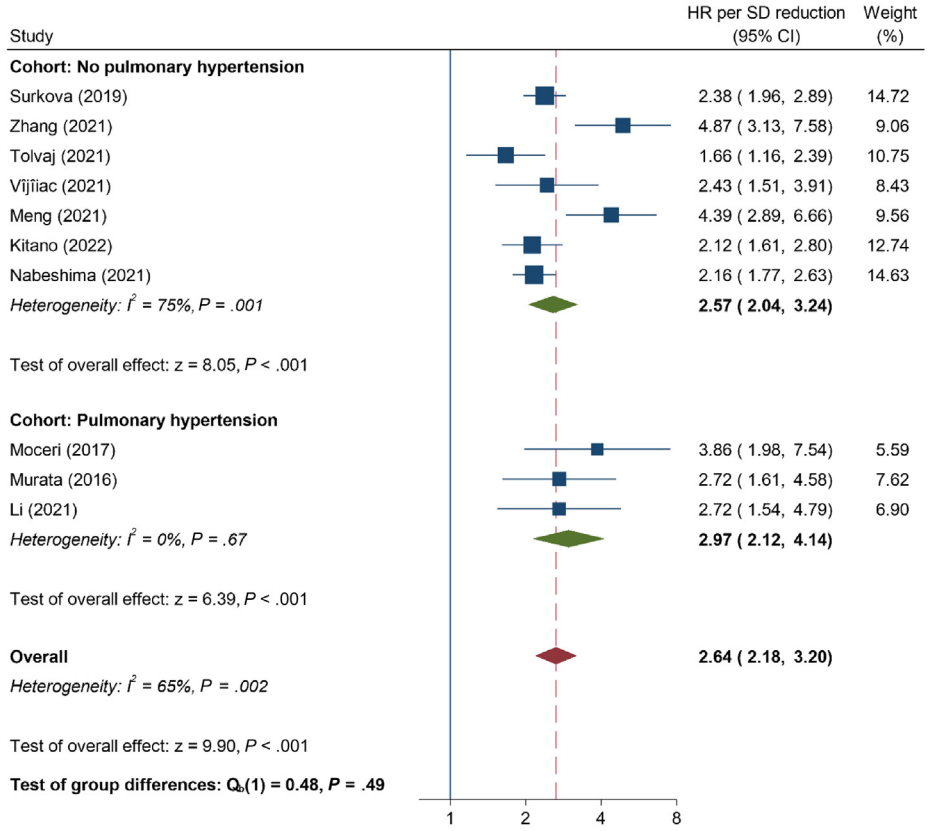
Data are presented as mean ± SD or median (interquartile range).



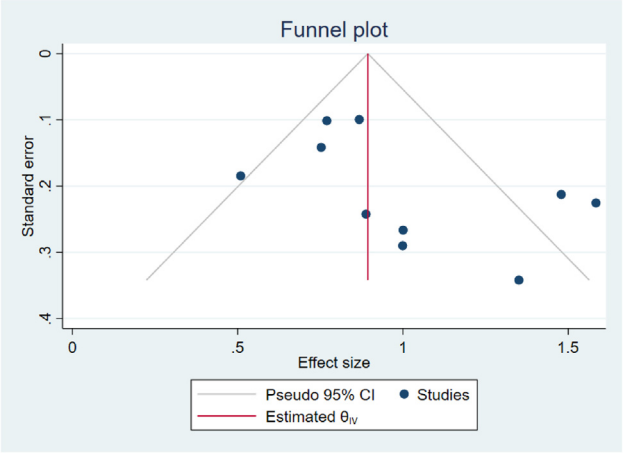
Supplemental Figure 1 Quality of included studies assessed using the QUIPS tool.



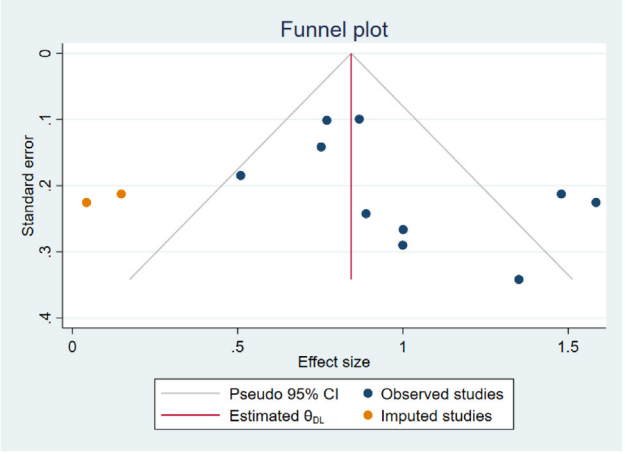
Supplemental Figure 2 Three-dimensional echocardiography–derived RVEF and its association with all-cause mortality. The HRs are per 1 SD reduction in RVEF according to each study. Accordingly, an HR of >1.00 means that a 1 SD reduction in RVEF is associated with increased risk of adverse events.



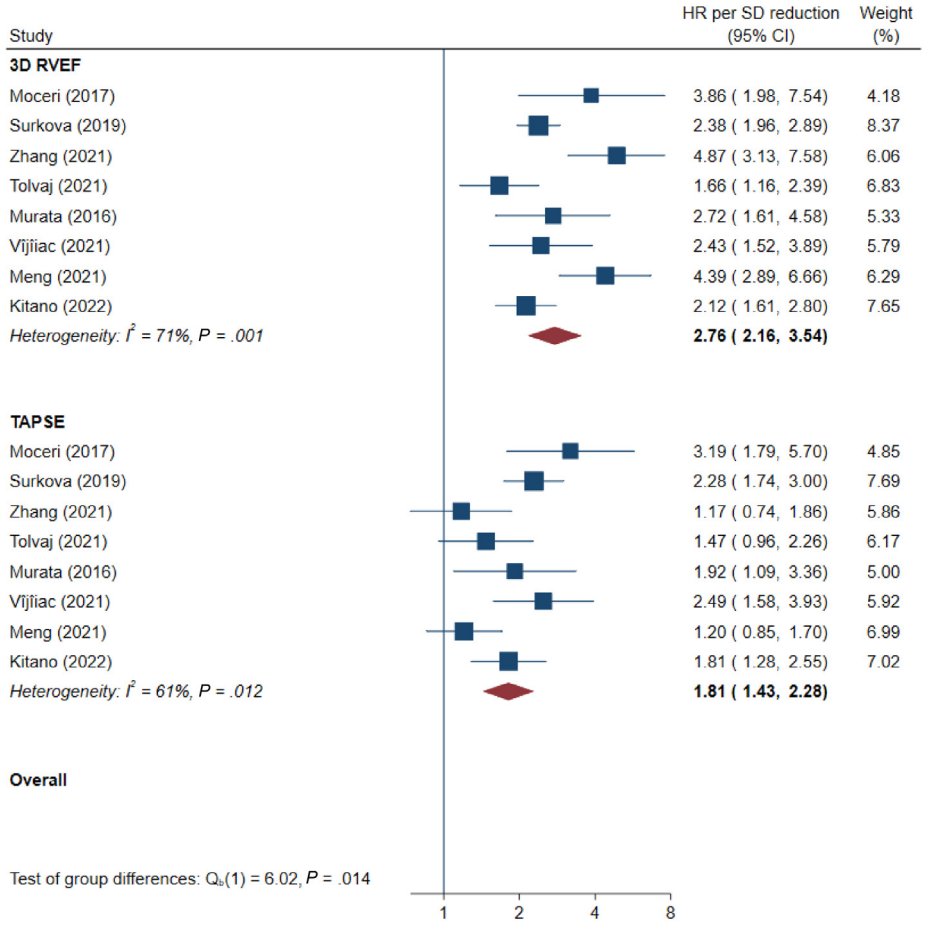
Supplemental Figure 3 Three-dimensional echocardiography–derived RVEF and its association with all-cause mortality and/or composite adverse cardiopulmonary end points: subgroup analysis of studies reporting outcomes on patients with a primary diagnosis of pulmonary hypertension versus those studies including patients with other cardiopulmonary conditions. The HRs are per 1 SD reduction in RVEF according to each study. Accordingly, an HR of >1.00 means that a 1 SD reduction in RVEF is associated with an increased risk of adverse events.



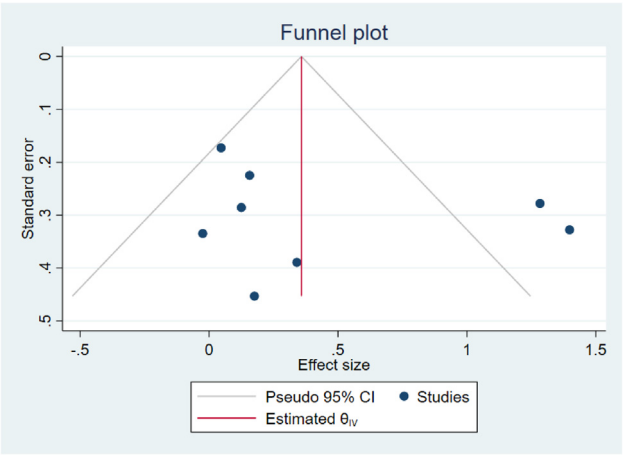
Supplemental Figure 4 Funnel plot of studies assessing 3D RVEF and its association with all-cause mortality and/or composite adverse cardiopulmonary events.



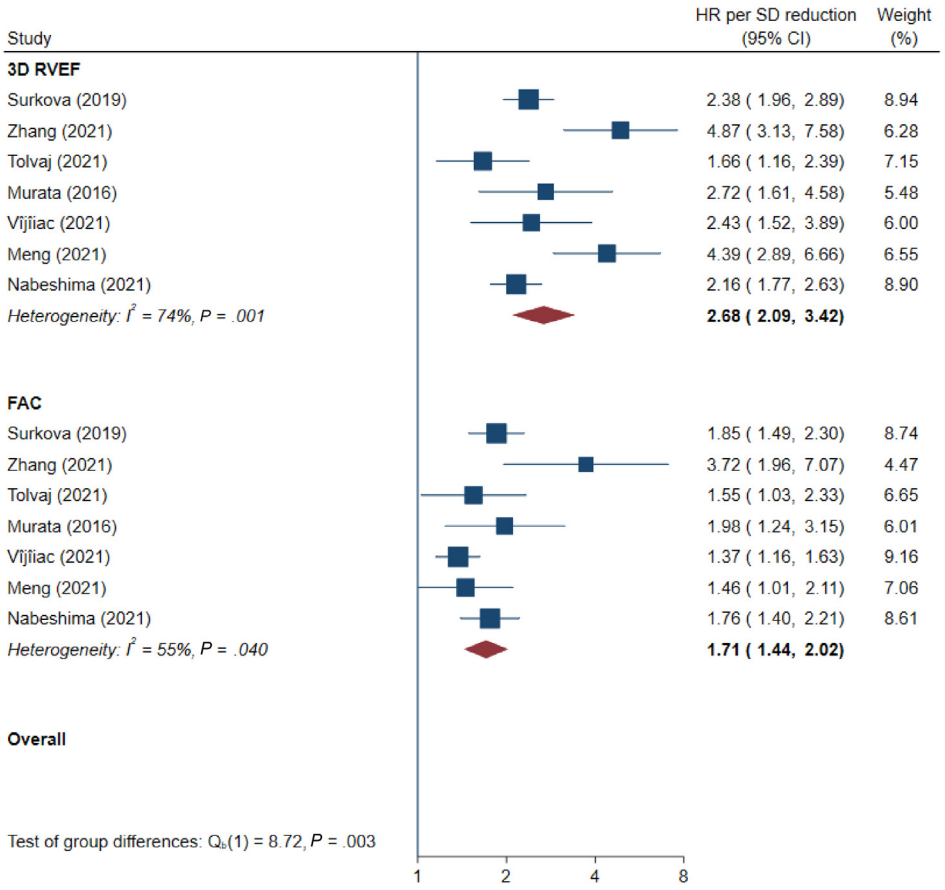
Supplemental Figure 5 Funnel plot and trim-and-fill analysis of studies assessing 3D RVEF and its association with all-cause mortality and/or composite adverse cardiopulmonary events. *Blue dots* represent the original data points (observed studies). The *2 orange dots* represent the 2 imputed study estimates in accordance with Duval and Tweedie trim-and-fill analysis using the G0 estimator. Accordingly, the *red line* represents the bias-adjusted overall estimate.



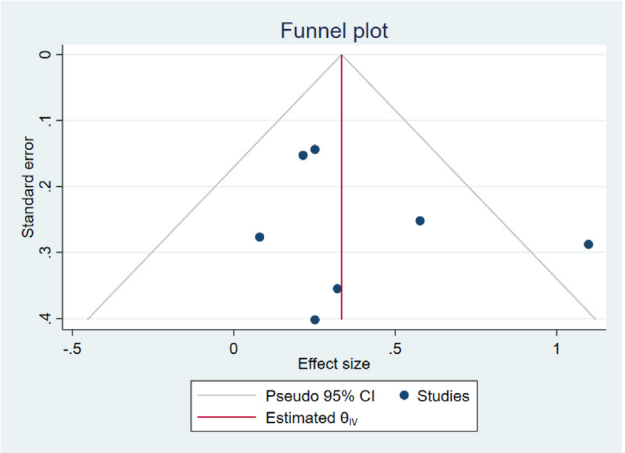
Supplemental Figure 6 Three-dimensional echocardiography–derived RVEF and TAPSE and their association with all-cause mortality and/or composite adverse cardiopulmonary end points. The HRs are per 1 SD reduction in RVEF or TAPSE according to each study. Accordingly, an HR of >1.00 means that a 1 SD reduction in RVEF or TAPSE is associated with an increased risk of adverse events.



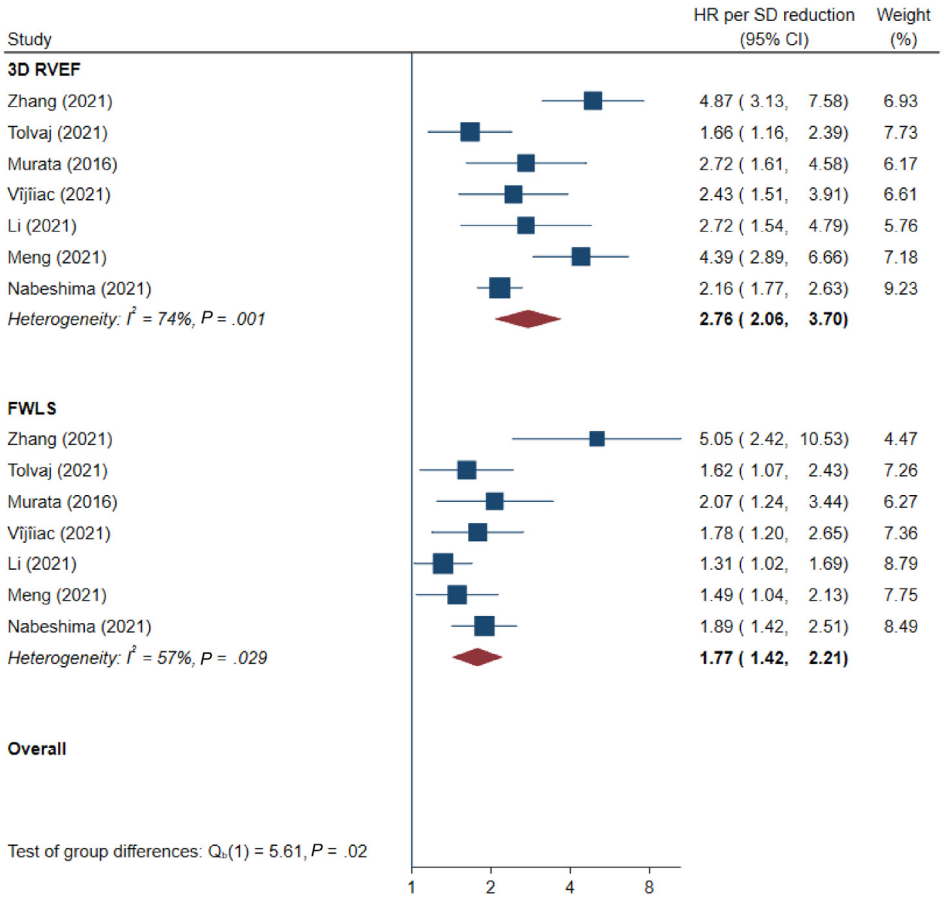
Supplemental Figure 7 Funnel plot of studies assessing 3D echocardiography–derived RVEF versus TAPSE and their association with all-cause mortality and/or composite adverse cardiopulmonary end points.



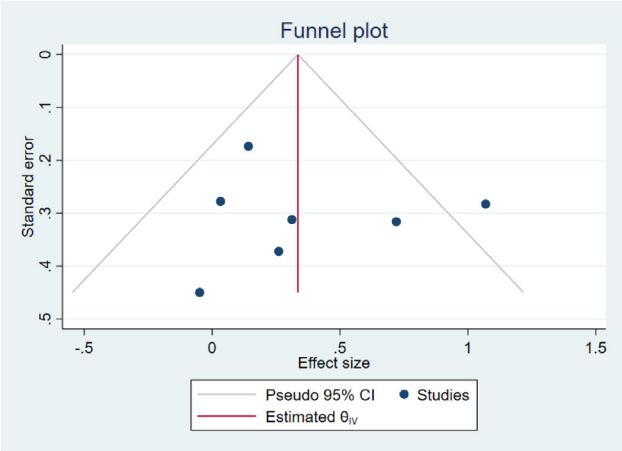
Supplemental Figure 8 Three-dimensional echocardiography–derived RVEF and FAC and their association with all-cause mortality and/or composite adverse cardiopulmonary end points. The HRs are per 1 SD reduction in RVEF or FAC according to each study. Accordingly, an HR of >1.00 means that a 1 SD reduction in RVEF or FAC is associated with an increased risk of adverse events.



Supplemental Figure 9 Funnel plot of studies assessing 3D echocardiography–derived RVEF versus FAC and their association with all-cause mortality and/or composite adverse cardiopulmonary end points.



Supplemental Figure 10 Three-dimensional echocardiography–derived RVEF and FWLS and their association with all-cause mortality and/or composite adverse cardiopulmonary end points. The HRs are per 1 SD reduction in RVEF or FWLS according to each study. Accordingly, an HR of >1.00 means that a 1 SD reduction in RVEF or FWLS is associated with an increased risk of adverse events.



Supplemental Figure 11 Funnel plot of studies assessing 3D echocardiography–derived RVEF versus FWLS and their association with all-cause mortality and/or composite adverse cardiopulmonary end points.