The Role of Speckle-Tracking Echocardiography in Predicting Mortality and Morbidity in Patients With Congenital Heart Disease: A Systematic Review and Meta-analysis

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Background: Speckle-tracking echocardiography (STE) is now routinely included in cardiac evaluations, but its role in predicting mortality and morbidity in congenital heart disease (CHD) is not well described. We conducted a systematic review to evaluate the prognostic value of STE in patients with CHD.

Methods: The EMBASE, Medline, Web of Science, Scopus, and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched from inception to January 2023 for terms related to all CHD, STE, and prognosis. Meta-analysis of association of right ventricle and left ventricle strain (RV S_I and LV S_I, respectively) with major adverse cardiovascular events (MACEs) was performed in atrial switch transposition of the great arteries (asTGA)/congenitally corrected TGA (ccTGA), tetralogy of Fallot (ToF), and congenital aortic stenosis (cAS)/bicuspid aortic valve (BAV). *P*-value combination analysis was additionally performed for all CHD groups.

Results: A total of 33 studies (30 cohorts, $n = 8,619$ patients, children, and adults) were included. Meta-analysis showed the following parameters as being associated with MACE: RV S_I in asTGA/ccTGA (hazard ratio [HR] = 1.1/%; CI, [1.03; 1.18]), RV S_I and LV S_I in ToF (HR = 1.14/%; CI, [1.03; 1.26] and HR = 1.14/%; CI, [1.08; 1.2], respectively), and LV S_I in cAS/BAV (HR = 1.19/%; CI, [1.15; 1.23]). The RV S_I and strain rate were associated with outcomes also in single ventricle/hypoplastic left heart syndrome (at all palliation stages except before Norwood stage 1) and LV S_I in Ebstein's anomaly.

Conclusions: This systematic review and meta-analysis showed that biventricular strain and strain rate were associated with outcomes in a variety of CHD, highlighting the need for updated recommendations on the use of STE in the current guidelines, specific to disease types. (J Am Soc Echocardiogr 2024;37:216-25.)

Keywords: Speckle-tracking echocardiography, Congenital heart disease, Tetralogy of fallot, Systemic right ventricle, Single ventricle, Meta-analysis

INTRODUCTION

Congenital heart disease (CHD) is the most common congenital defect, affecting approximately 1% of all births worldwide and encompassing a diverse spectrum of distinct pathologies.[1] Extraordinary advances in the field have led to improved survival, with an increasing adult population living with CHD,[2] which also means an increased morbidity burden and a need for better risk stratification tools.

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Dan M. Dorobantu is supported by a doctoral scholarship (grant MR/N0137941/1 for the GW4 BIOMED DTP, awarded to the Universities of Bath, Bristol, Cardiff, and Exeter from the Medical Research Council/United Kingdom Research and Innovation). Nurul H. Amir is supported by the government of Malaysia under the Majlis Amanah Rakyat agency. Curtis A. Wadey is supported by an industrial PhD studentship from the University of Exeter and Canon Medical Systems UK.

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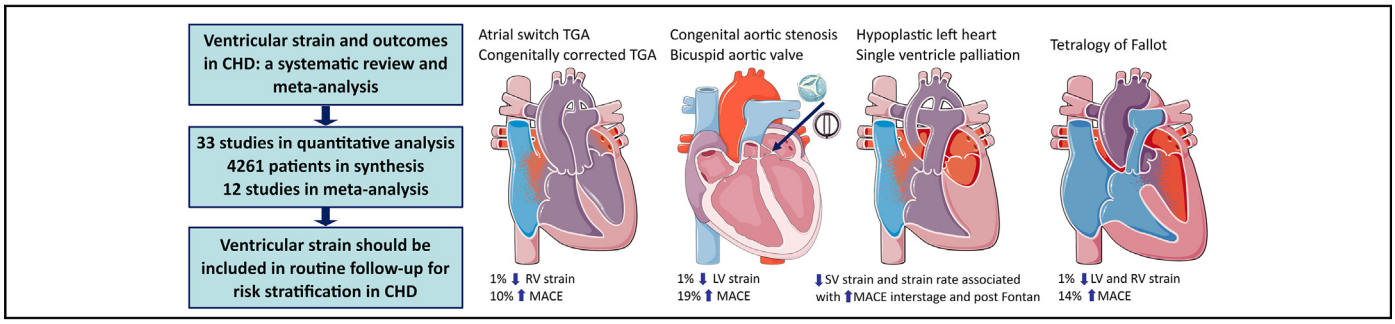
0894-7317

https://doi.org/10.1016/j.echo.2023.11.003



Central Illustration Left ventricle, RV, and SV strain and strain rate are associated with cardiac outcomes (MACE) in CHD such as systemic RV transposition of the great arteries (TGA), SV, cAS, or ToF and should be included in risk stratification during follow-up.

Speckle-tracking echocardiography (STE) is now an established tool in acquired heart disease, allowing accurate quantification of myocardial mechanics.[3] There is a large body of high-quality evidence supporting the role of ventricular strain in pathologies such as heart failure,[4] ischemic heart disease,[5] chemotherapy surveillance,[6] valvopathies,[7] and cardiomyopathies.[8] In CHD, STE has the advantage of fewer geometrical constraints, while strain rate could allow for less load-dependent measurements of myocardial performance compared with strain or volumetric measures such as ejection fraction,[9] potentially useful in pre- and postsurgical assessment.

Current European Society of Cardiology[10] and American College of Cardiology/American Heart Association[11] guidelines for the management of adult CHD do not provide disease-specific recommendations on the use of STE, nor do they describe its use in risk stratification. Pediatric CHD guidelines recommend STE still as a novel useful technique, focusing on the structural rather than functional assessment.[12,13] To date, there is no summary of the available evidence on the use of STE in CHD risk stratification, despite the increasing interest in the topic.

To address this gap in knowledge and contribute to future guideline recommendations, we aimed to investigate the current data available on ventricular STE in outcome prognosis for patients with CHD, using a systematic review and meta-analysis methodological approach.

METHODS

This study was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and the protocol was submitted prospectively to the International Prospective Register of Systematic Reviews (PROSPERO; CRD42021268161).[14]

Database Search and Study Eligibility

EMBASE, Medline, Web of Science, Scopus, and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched from inception to January 2023. The search strategy included terms related to "morbidity, mortality, outcomes," "congenital heart disease," "speckle tracking," and "echocardiography." The full search strategy is available in the Appendix.

Inclusion criteria were (1) any diagnosis of CHD; (2) two-dimensional STE with measurements of ventricular systolic function, left (LV), right (RV), or single ventricle (SV); (3) clinical outcomes defined as death, resuscitation, cardiac transplant, cardiac reintervention (surgical/catheter), hospitalization, clinical worsening, arrhythmia, or a composite outcome of any of the above (major adverse cardiovascular events [MACEs]); (4) a research question assessing the association between STE and MACE.

Exclusion criteria were (1) heart transplant; (2) fetal echocardiography; (3) pulmonary hypertension cohort; (4) non-CHD pathology; (5) aorthopathies unless part of bicuspid aortic valve (BAV); (6) circulatory assist devices; (7) tissue Doppler, magnetic resonance imaging, or three-/four-dimensional based strain; (8) research questions not aimed at predicting morbidity and/or mortality using STE; (9) abstracts with no published full text, case reports, reviews, editorials or position papers; (10) non-English-language articles.

Study Selection and Screening

Title, abstract, and full text screening were performed using Covidence (Veritas Health Innovation) by 4 reviewers (D.M.D., N.H.A., C.A.Wadey, and C.S.), in pairs, with discrepancies resolved by full consensus. Studies were grouped by disease: systemic RV in atrial switch transposition of the great arteries (asTGA) or congenitally corrected TGA (ccTGA), repaired tetralogy of Fallot (ToF), BAV or congenital aortic stenosis (cAS), hypoplastic left heart syndrome (HLHS) at several treatment points (pre–stage 1/Norwood, post–stage 1/Norwood, pre–stage 2/Glenn, and post–stage 2/Glenn), SV after Fontan operation, Ebstein's anomaly, and coarctation of the aorta (CoA). There were 3 cohorts described in 2 studies each in ccTGA,[15,16] SV,[17,18] and cAS/BAV.[19,20] Of these duplicate studies all were described in the synthesis without meta-analysis (SWiM) analysis, but only the larger (or that reporting the effect measure of interest) was included in the subsequent analysis. Authors were contacted with the opportunity to confirm that studies described the same cohort where this was not clear.

Data Extraction

Data extraction was conducted independently by 4 reviewers and included the following.

Abbreviations

asTGA = Atrial switch transposition of the great arteries

BAV = Bicuspid aortic valve

cAS = Congenital aortic stenosis

ccTGA = Congenitally corrected transposition of the great arteries

CHD = Congenital heart disease

CoA = Coarctation of the aorta

HLHS = Hypoplastic left heart syndrome

HR = Hazard ratio

LV = Left ventricle

MACE = Major adverse cardiovascular event

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RoB = Risk of bias

RV = Right ventricle

Sc = Circumferential strain

S_l = Longitudinal strain

S_r = Radial strain

SR_c = Circumferential strain rate

SR_l = Longitudinal strain rate

SR_r = Radial strain rate

STE = Speckle-tracking echocardiography

SV = Single ventricle

SWiM = Synthesis without meta-analysis

ToF = Tetralogy of Fallot

Study Characteristics. Study characteristics included the original title, author list, year of publication, study design, country of patient population, journal, type of CHD, and use and type of intervention.

Participants. Participant data included total number, number with disease of interest, gender, age, follow-up time, and associated clinical data reported (functional status, associated diseases, etc.).

Echocardiographic Strain-Derived Measurements of Interest. Left ventricle, RV or SV longitudinal strain (S_l), circumferential strain (S_c), radial strain (S_r), and the corresponding strain rate (SR_l, SR_c, SR_r) were extracted as main parameters of interest. Other strain-derived parameters such as torsion, rotation, and dyssynchrony parameters were extracted, but we did not find any that were reported in 2 studies on the same disease, so these were not reported here.

Outcomes. The study outcomes were hazard ratio (HR)/relative risk/odds ratio for clinical outcomes (cardiac or all-cause death, heart transplant, ventricular arrhythmias, need for circulatory support, other arrhythmias, need for hospitalization, disease progression or specific complications, functional class, worsening of clinical status, reintervention) and summary of STE measurements and outcomes when a relative risk estimate was not provided (such as mean difference between events and no events).

Risk of Bias Assessment

Risk of bias (RoB) was assessed independently by 2 reviewers, and the final score given by consensus of 4, using the Quality in Prognosis Studies tool.[21] This interrogates 6 domains: (1) study participation, (2) study attrition, (3) prognostic factors, (4) outcome measurement, (5) study confounding, and (6) statistical analysis. Results are presented visually, each study being graded as low, moderate, and high RoB. Publication bias was assessed using visual inspection of funnel plots and Egger's test for small study bias. For all other studies the proportion of conventionally statistically significant ($P < .05$) studies from the total was reported, due to heterogeneity in reporting of effect sizes precluding other methods.

Statistical Analysis

Pooled frequencies are presented as numbers and percentages, and continuous values as means ±SD. To calculate pooled mean ages, any median values (with interquartile range or range) were first transformed to means ± SD, and then the distributions were sequentially combined per Cochrane recommendations, shown if nonmissing in at least 2.[22]

Random-effect Der Simonian–Laird meta-analysis with 95% CI was performed on log-transformed HR data. Hazard ratios for meta-analyses were expressed per percentage increase of strain, which is on a negative scale (more negative is better). If studies reported strain on an absolute scale, then HRmetanalysis = 1/reported HR. If studies reported standardized absolute values, then HRmetaanalysis = exp(ln(1/reportedHR)/SD of strain parameter). The same transformations were done on lower and upper 95% interval limits. Where 95% CIs were missing, these were calculated using the Cochrane recommended formulas.[22] Data were pooled for meta-analysis only where there was the same disease and same type of STE parameter reported in 3 or more studies.

Where there was insufficient information to warrant meta-analyses, data were summarized according to the SWiM guidelines.[23] If 2 or more studies with the same disease and STE parameter were found, data were summarized by combining *P* values, using Fisher's method,[24] with the chi-square statistic and resulting *P* value being reported. Comparisons between the predictive value of STE parameters over other risk factors were summarized narratively for each study, when reported. Statistical analyses were conducted using STATA/SE 12 (StataCorp LP). The central illustration uses Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license.

RESULTS

A total of 33 studies (30 cohorts) were included (Figure 1). Study descriptions, reported STE measurements, and their associations with MACEs are summarized in Supplementary Tables S1 and S2. One study reporting combined CHD, by Egbe et al. (2022),[25] was only included in the descriptive Supplementary Tables S1 and S2 and not in the subsequent synthesis analyses.

There were 4,261 patients in total (neonate to adults) spanning 6 diagnosis groups. The most reported STE parameters overall were RV/SV S_l ($n = 20$ studies) and LV S_l ($n = 15$) followed by RV/SV SR_l ($n = 10$), RV/SV S_c ($n = 7$), RV/SV SR_c ($n = 6$), and $n = 1$ each for LV SR_l, LV S_c, LV S_r, and RV S_r. There were 15 cohorts reporting various diastolic, dyssynchrony, or atrial strain measurements, which were not the focus of the study and were not analyzed.

Systemic RV—asTGA and ccTGA

There were 6 studies (5 cohorts) with asTGA and ccTGA ($n = 572$; mean age, 36.5 ± 12.8 years). Of these, $n = 255$ patients had asTGA (mean age, 31.6 ± 7.2 years) and $n = 317$ had ccTGA (mean age, 40.5 ± 14.8 years). There was evidence of strong associations between RV S_l and LV S_l and outcomes for asTGA/ccTGA in at least 1 study ($P < .0001$ and $P = .002$, respectively, Table 1). The meta-analysis showed that worse RV S_l was negatively associated with MACE, with a univariable HR of 1.1/% (CI, 1.03; 1.18; Figure 2A), and a multivariable HR of 1.12/% (CI, 1.0; 1.25; Figure 2B). Of the 6 studies, 4 analyzed and reported the added prognostic value of RV S_l to conventional parameters, and of these, 3 found improved

HIGHLIGHTS

- Ventricular strain is associated with outcomes in CHD.
- Interstage, not postnatal, ventricular strain is associated with outcomes in HLHS.
- STE recommendations should be disease specific.
- STE has added prognostic value to conventional risk factors in CHD.
- Better, more inclusive research is needed to improve STE use recommendations.

predictive values of models including RV S_I and 1 found no difference compared with those including RV fractional area change (Supplementary Table S3).

Repaired ToF

There were 5 studies included on ToF (n = 1,038; mean age, 26.1 ± 17.8 years; n = 876, 30.3 ± 16.4 years excluding 1 early post-operative study). There was evidence of associations between RV S_I and LV S_I and outcomes in at least 1 study ($P < .0001$ for both; Table 1). A meta-analysis of 3 studies showed that worse RV S_I (Figure 2C; HR = 1.14/%; CI, [1.02; 1.26]) and worse LV S_I (Figure 2D, HR = 1.14/%, CI, [1.08; 1.2]) were both associated

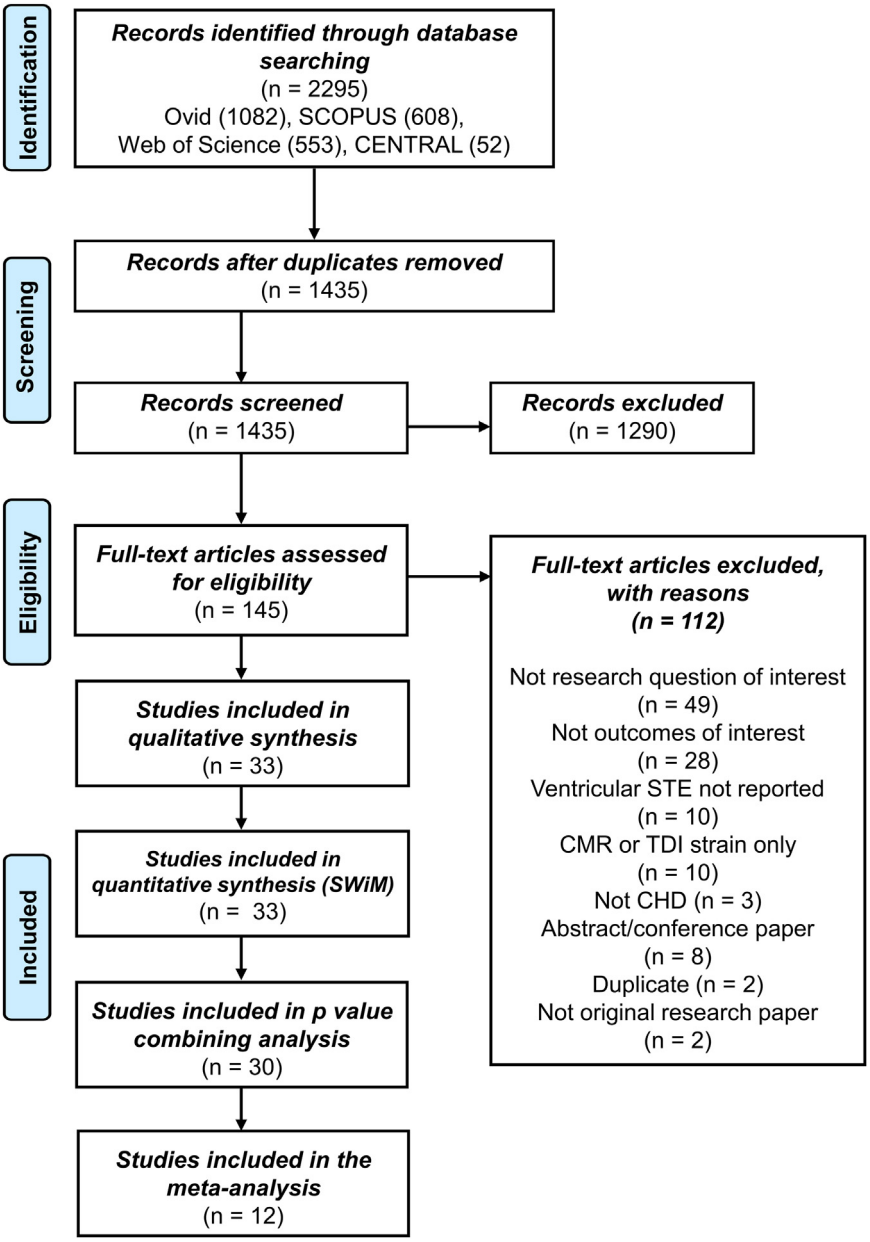


Figure 1 PRISMA flowchart of screened, included, and excluded studies.

Table 1 Associations of STE parameters with outcomes in CHD by disease type (summary of *P* values combination analysis)

	*n**	Chi squared	*P* value
RV S_l/SV S_l	27		
asTGA/ccTGA	6	52.2	<.0001
Corrected ToF	4	46.1	<.0001
HLHS pre–stage 1/Norwood	3	8.8	.2
HLHS post–stage 1/Norwood	3	29.5	.0002
HLHS pre–stage 2/Glenn	3	28.2	<.0001
HLHS post–stage 2/Glenn	2	21.3	<.0001
SV after Fontan	3	37.7	<.0001
LV S_l	17		
BAV/cAS	5	44.1	<.0001
Corrected ToF	4	48.7	<.0001
asTGA/ccTGA	3	20.3	.002
Ebstein	3	27.8	.0001
RV SR_l/SV SR_l	16		
HLHS pre–stage 1/Norwood	3	6.8	.3
HLHS post–stage 1/Norwood	3	19.4	.004
HLHS pre–stage 2/Glenn	3	27.9	<.0001
HLHS post–stage 2/Glenn	2	20.8	.0003
SV after Fontan	3	17.5	.008
RV S_c/SV S_c	10		
HLHS pre–stage 1/Norwood	2	7	.1
HLHS post–stage 1/Norwood	2	9.2	.01
SV after Fontan	3	35.6	<.0001
RV S_c/SV SR_c	9		
HLHS pre–stage 1/Norwood	2	3.5	.5
HLHS post–stage 1/Norwood	2	9.2	.01
SV after Fontan	3	37.1	<.0001

Only disease/STE parameter pairs with 2 or more studies are shown.
*Number of *P* values, which include subgroups from the same study (e.g., asTGA, ccTGA, or HLHS palliation stages).

with MACE. Of these 5 studies, 4 reported on the added prognostic role of STE to conventional parameters, and all found improvements in predictive values of models when including RV or LV strain (Supplementary Table S3).

Congenital Aortic Stenosis/BAV and CoA

Five cohorts were included on cAS or BAV ($n = 952$, of which 92 looked specifically at BAV associated arthropathy), with a mean age of 42.8 ± 18.4 years. There was evidence of associations between LV S_l and outcomes in at least 1 study ($P < .0001$; Table 1). The meta-analysis showed that worse LV S_l was negatively associated with MACE, with a univariable HR of 1.19/% (CI, 1.15; 1.23; Figure 2E), and a multivariable HR of 1.09/% (CI, 1.05; 1.14; Figure 2F). Of the 5 cohorts, 4 reported on the added prognostic role of STE to conventional parameters and 3 found added predictive value when including LV S_l (Supplementary Table S3).

There was only 1 study ($n = 821$) evaluating the role of LV S_l in predicting outcomes in CoA patients, which found that LV and RV strain were independently associated with MACE, within a validated risk score (Supplementary Table S3).

Hypoplastic Left Heart Syndrome—Stages 1 and 2 and SV After the Fontan Procedure

There were 8 studies (7 cohorts) included with HLHS or HLHS variants ($n = 256$), with imaging done at various stages of treatment (Supplemental Tables S1 and S2). Based on all 10 HLHS and SV cohorts, evidence of associations at different treatment stages was evaluated, as reported in Table 1. There was no evidence of associations between RV S_l, RV S_c, RV SR_l, or RV SR_c and outcomes when evaluated pre–stage 1/Norwood ($P = .18$, $P = .1$, $P = .3$, and $P = .5$, respectively). There was evidence in at least 1 study of strong associations between RV S_l, RV SR_l, RV S_c, and RV SR_c and outcomes when measured shortly after the stage 1/Norwood procedure ($P = .0002$, $P = .004$, $P = .01$, and $P = .01$, respectively), between RV S_l and RV SR_l and outcomes when measured pre–stage 2/Glenn ($P < .0001$ for both), and between RV S_l and RV SR_l and outcomes when measured post–stage 2/Glenn ($P < .0001$ and $P = .0003$, respectively). Of the 7 studies reporting interstage outcomes, 5 report enough data to compare STE to other parameters in terms of association with outcomes, and in 4 of these there was evidence of S_l, SR_l, or both having superior predictive value over conventional parameters (Supplementary Table S3). There was also evidence of strong associations between SV S_l, SV SR_l, SV S_c, and SV SR_c and outcomes in at least 1 study when measured after the Fontan operation ($P < .0001$, $P = .008$, $P < .0001$, and $P < .0001$, respectively). Of the 3 studies including Fontan patients, only 1 reported sufficient data on the added predictive value of S_c (Supplementary Table S3).

Ebstein's Anomaly

There were 3 cohorts included on Ebstein's anomaly ($n = 82$ neonatal patients, $n = 673$ adult patients), with a mean age of 4.4 ± 5.7 days and 37 ± 17.8 years, respectively. There was evidence to suggest strong associations of LV S_l to outcomes in at least 1 study ($P = .0001$; Table 1). Only 1 of these studies investigated the prognostic role of STE compared to conventional parameters and found that LV S_l improved the predictive value when added to LVEF (Supplementary Table S3).

Risk of Bias Assessment

The RoB of included studies varied significantly by specific disease type (Figure 3). Studies on asTGA/ccTGA had lower ($P = .01$) RoB (100% low RoB), compared with HLHS (85% moderate and 15% high RoB), SV Fontan (33% moderate and 66% high RoB), and ToF (40% moderate and 20% high RoB). Small study publication bias in the meta-analysis is likely, as shown by the funnel plots (Figure 4A and C), predominately due to asTGA/ccTGA studies (Figure 4B). Sensitivity analysis shows that after excluding asTGA/ccTGA studies, there was no longer a small studies effect (Egger test *P* value = .9). When considering all studies included in the *P* value combining analysis, 58.3% of reported effects were statistically significant, and 41.7% were not, with only HLHS pre–stage 2/Glenn and ToF showing significantly more positive associations (80%), which could suggest publication bias.

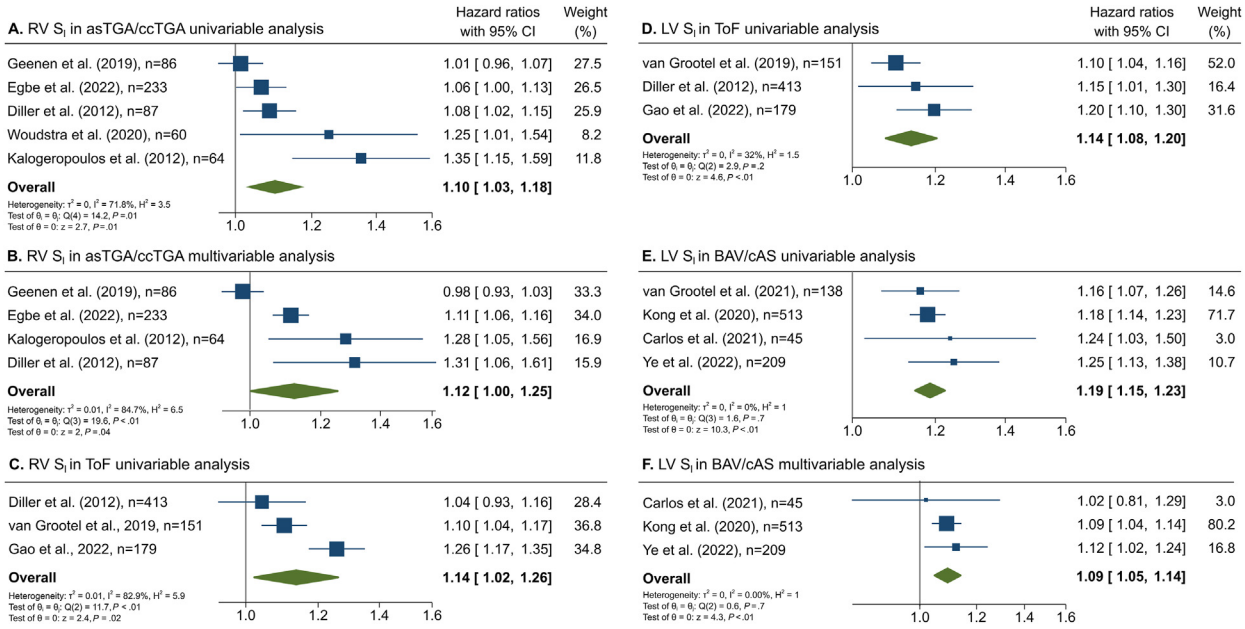


Figure 2 Meta-analysis associations between RV and LV S_l with MACE outcomes in CHD. **(A)** Associations between RV S_l (free wall or global) and MACE in asTGA and ccTGA, from univariable analysis. **(B)** Associations between RV S_l (free wall or global) and MACE in asTGA and ccTGA, from multivariable analysis. **(C)** Associations between RV S_l and MACE in ToF, from univariable analysis. **(D)** Associations between LV S_l and MACE in ToF, from univariable analysis. **(E)** Associations between LV S_l and MACE in BAV and cAS, from univariable analysis. **(F)** Associations between LV S_l and MACE in BAV and cAS, from multivariable analysis.

DISCUSSION

This systematic review and meta-analysis showed that ventricular strain and strain rate can be used in risk stratification for CHD and can add to the role of conventional imaging and clinical parameters, but the quality and number of studies vary by disease. Right ventricle S_l was associated with MACE in asTGA/ccTGA and corrected ToF, and LV S_l in BAV/cAS and corrected ToF. Single ventricle strain and strain rate were associated with outcomes in HLHS, during the interstage period, and after stage 2/Glenn and Fontan, but not before stage 1/Norwood. These findings support the use of ventricular STE for risk stratification in CHD follow-up, in addition to well-established parameters, and should encourage more research into the topic (Central Illustration).

Role of STE in CHD Outcome Prediction

In CHD the ventricle anatomy is often complex, with volumetric and loading condition constraints, making myocardial strain and strain rate attractive alternatives for cardiac function assessment[9,26,27] and, importantly, for ventriculoarterial coupling.[28]

In this systematic review we found that longitudinal systolic strain was the most commonly reported STE measurement, and this reflects both clinical practice and current general echocardiography guidelines.[29] Both RV and LV strain were previously found to be abnormal in a variety of CHD[30] and predict outcomes in other acquired heart disease.[4,5,7,31] Strain rate was proposed as less affected by loading conditions compared with geometric-based measures such as strain and ejection fraction.[26,27] This strain rate option could be of use in perioperative risk stratification,[30] especially in complex conditions where staged repairs imply dramatic changes to hemodynamic conditions, such as HLHS, when assessing ventriculoarterial coupling could be of interest given the changes in pre- and afterload.[28]

Systemic RV—asTGA and ccTGA. Right ventricle S_l (global) was associated with MACE in CHD with systemic RV, with an increase of MACE probability of 10% to 12% for each 1% worsening of RV S_l, independent of other conventional parameters. These findings support the reporting of RV strain in the regular evaluation of these patients for the purpose of identifying individuals at high risk. Future research should report both global and free wall strain values, to provide better-quality data on the prognostic role and impact of regional function and dyssynchrony on outcomes. Importantly, RV strain has been shown to be a better prognostic factor compared with other measures of RV function in the presence of functional tricuspid regurgitation,[32] and it is reasonable to assume this would also be true for systemic RV.

While atrial switch techniques are no longer recommended for the treatment of TGA, rare special indications remain, which would add to the already existing adult population.[33] In both cases complication rates are cumulatively high with age, and noninvasive prognostic factors could guide early therapy escalation, including heart transplant listing or risk stratification for sudden cardiac death.

Hypoplastic Left Heart Syndrome and Other SV—Different Uses at Different Stages. The geometry of the SV does not correspond to the current LV or RV models, and its loading conditions vary from pressure overload to volume overload and can have different shunting present. Hemodynamic conditions change between palliation stages and can even change dramatically with the clinical status, frequently between birth and stage 1/Norwood.[34]

Speckle-tracking echocardiography could be very useful in these circumstances, where commonly used parameters are limited by geometrical, angle, and loading conditions. Measures of cardiac function that are less geometric shape dependent, such as S_l and S_c, could better assess SV function changes through treatment stages. Due to the heterogeneity of SV anatomical variants, methods of cardiac

Figure 3 Risk of bias for included studies was assessed, and proportion of overall low RoB varied by disease type.

function assessment, which do not include any assumptions of cardiac chamber shape and allow for individual segmental evaluation, for example, STE, can have numerous uses in detailed evaluation of these complex patients. In all studies reporting interstage and post-Glenn assessments, SV/RV strain was found to be associated with outcomes. Strain rate, described to be less load dependent compared with ventricular strain or ejection fraction,[26,27] was consistently associated with outcomes when measured interstage and would even appear to outperform strain. Currently, there are still limited data on the usefulness of strain rate–derived parameters in clinical scenarios, especially in children with higher heart rates affecting data quality. With increasing imaging frame rates in recent years, strain rate should become more reliable, and research into its use should be encouraged, especially as part of multimodal cardiac function assessment.

Interestingly, STE parameters measured before stage 1/Norwood were not shown to be associated with outcomes, suggesting the driver of early mortality before palliation might not be cardiac function but rather hemodynamic instability and inadequate pulmonary or systemic perfusion due to critical lesions. As such, evaluation of cardiac function through STE might be best used after stage 1/Norwood, to identify patients at high risk and guide timings and indications of subsequent procedures, rather than immediately after birth. After the Fontan operation, evidence of the prognostic role of STE is also limited to 3 studies, which report discrepant results. Nevertheless, the larger of the 3 studies shows a positive association of dominant ventricle strain to outcome, which should encourage serial evaluation of SV strain in these patients to guide treatment escalation.

Tetralogy of Fallot—Biventricular Function Role. Surprisingly, despite well-described biventricular dysfunction in ToF and the proposed role of both ventricular dyssynchony and LV dysfunction in the pathological mechanisms leading to sudden cardiac death,[35] only 4 studies evaluated the role of STE in predicting mid-/long-term MACE in this group.

Results were consistent, with all reporting at least 1 STE parameter associated with at least 1 definition of MACE, and the meta-analysis showed both RV S_I and LV S_I to be prognostic of MACE, independent of other conventional parameters, including QRS duration. Current volumetric cutoffs for pulmonary valve replacement might not offer the best outcomes possibly due to already irreversible RV dysfunction,[36] with later interventions showing worse survival.[37] Thus, biventricular strain should be included in the current risk stratification criteria, to supplement current volume-based cutoffs, and potentially lead to better timing of pulmonary valve replacement.

Bicuspid Aortic Valve and cAS—Role of LV Strain. The current meta-analysis shows that LV strain is prognostic of MACE in BAV/cAS, and this is in line with degenerative aortic stenosis, where LV STE is used widely in practice.[7] However, there was no evidence to support the use of LV STE as a predictor for outcomes related to BAV aortopathy. As such, evaluation of BAV/cAS should include LV strain for the purpose of MACE risk stratification and to inform the timing for aortic valve intervention, similarly to how STE is used in degenerative aortic stenosis.[7]

Current Recommendations on the Use of STE in CHD

Despite STE being available for clinical use for almost 2 decades, with day-to-day applications in general cardiology wards and high-quality evidence supporting ventricular strain as an independent predictor for outcomes in heart failure, valvopathies, and ischemic heart disease,[4,5,7,31] its role has not yet been clearly established in CHD. Both the European Society of Cardiology and the American College of Cardiology/American Heart Association recent guidelines for the management of adult CHD briefly mention STE as an available tool.[10,11] Pediatric CHD echocardiography guidelines also recommend STE as one of the novel, useful techniques but continue to be focused on structural evaluation rather than advanced functional assessment.[12,13] There is a gap in practice between general cardiology and CHD practice, owing to the limited body of data that is available, which needs to be addressed.

This current systematic review provides valuable insight into what is known, what gaps in knowledge remain, and based on these, what future steps might be taken to improve recommendations on STE use in CHD (Table 2). There is a gap in practice between other areas of cardiology and CHD, in the use of STE, and the only way forward to close this gap is for better-quality research to be a priority. New advances in STE, such as improved ease of use, shorter postprocessing

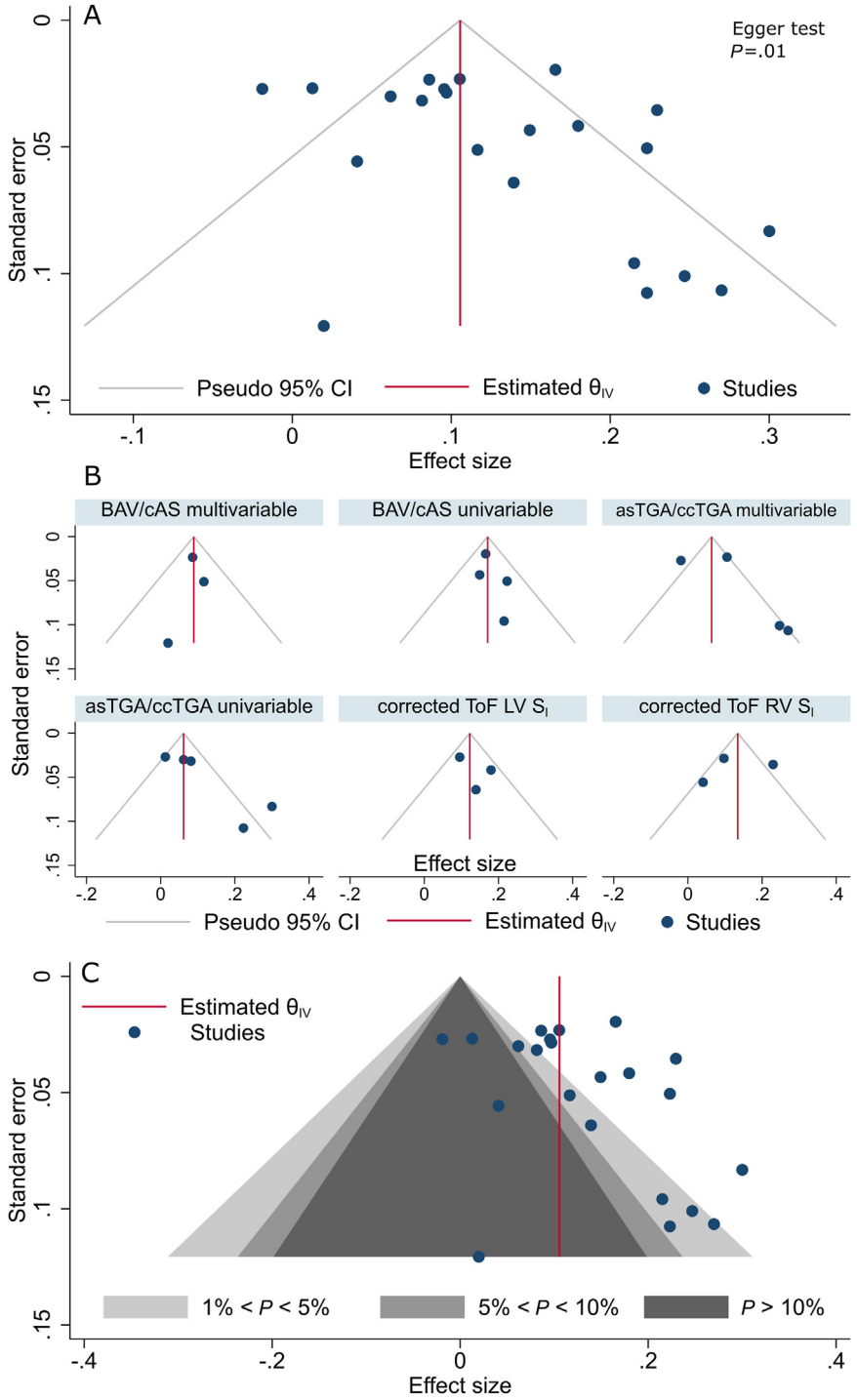


Figure 4 Publication bias risk in studies included in meta-analysis (univariable and multivariable). Funnel plot showing significant asymmetry overall **(A)** and by disease and analysis subgroups showing asymmetry predominantly in asTGA/ccTGA studies **(B)**. **(C)** Contour-enhanced funnel plot showing a disproportion between significant and nonsignificant effects being reported.

time, and better image quality, should make it easier to use this technique in the future. Some limitations that are inherent to complex imaging in CHD, such as anatomical diversity, small sample size, or unique hemodynamic conditions, will always present challenges and barriers when designing research projects, and we should also be conscious of this when evaluating available evidence.

Limitations

Congenital heart disease encompasses a wide variety of conditions, and this is reflected in the heterogeneity of the included cohorts, which can affect the interpretation of results in a meta-analysis. Similarly, there is variability in how STE measurements are performed and reported,[3] which limited the number of studies included in the pooled HR

Table 2 Prognostic role of STE in CHD—main findings, remaining gaps in knowledge, and future steps

Main findings—systematic review and meta-analysis
In adults asTGA/ccTGA, surgically corrected ToF and cAS/BAV, and RV S_l and LV S_l are associated with outcomes and can have a role in risk stratification.
In HLHS and other SV, both STE-derived S_l/S_c and SR_l/SR_c have potential use in interstage risk stratification and management but not before Norwood/stage 1.
Overall, STE-derived cardiac function measurements appear to have added prognostic value to conventional echocardiographic and clinical parameters in CHD.
Remaining gaps in knowledge
Among CHD types, there is variability in the volume and quality of data available, and this limits the interpretation of results and results in considerable RoB.
There are few studies aimed at pediatric populations, where using hard outcomes such as MACE would require large multicentric collaborations.
STE-derived strain rate could have potential uses in more complex CHD scenarios, such as pre-post operative assessment, but this role has yet to be established, along with standard protocols for assessment.
Data on the prognostic role of STE in SV palliation and especially after the Fontan procedure are limited and of moderate RoB, limiting adoption and future use.
There are CHD types where there are either few or no studies investigating the role of STE in risk stratification, such as Ebstein's syndrome, CoA, septal defects, etc.
Due to the use of MACE, and its variable definitions, it is not known whether different outcomes (death, arrhythmias, heart failure, reintervention, etc.) show different associations with STE-derived parameters.
Future directions
Prioritize prospective or large registry type clinical studies in CHD, especially in pediatric age groups, to allow for less biased, more inclusive, and more generalizable reports.
Focus on assessing the added prognostic value of STE-derived cardiac function parameters to those currently used in practice, in different CHD groups.
Encourage the reporting of STE-derived parameters in future outcome research, to improve the body of data available.
Identify the potential for collaborative research in pediatric CHD to allow for the use of more appropriate outcomes (primary hard outcomes, secondary soft outcomes) and target less common CHD types.
Reevaluate the guidelines and recommendations on how STE is used and reported in CHD clinical practice to reflect new data in the field and close the gap in practice between CHD and other areas of heart failure.

analysis. A MACE was defined differently in some studies, and to ensure simplicity, all of these events were considered in the pooled analysis, with a subanalysis of specific outcomes not being possible. This limited any inference on specific relations to outcomes such as sudden cardiac death or reintervention. Using a MACE outcome, less common in most pediatric CHD, likely biased the analysis to more adult studies, with the exception of HLHS. In addition, many of the included studies had a wide MACE definition that included such events like heart failure, hospitalization for heart failure, myocardial dysfunction, or reintervention, which can influence the interpretation of results. Meta-analysis of multivariable results was included in the final report, with the limitation that methodologies varied significantly among included studies. To maximize the use of available data, a *P*-value combination approach was used to summarize findings in addition to meta-analysis and SWiM, which is among the Cochrane recommended synthesis methods,[22] but limited to general interpretation that evidence exists for the association, rather than a clear quantification of the effect.

The RoB was lower in some CHD, especially SV or HLHS, and while this reflects not just the quality of the included work but also the limitations of the disease group, it still leads to limitations in how the evidence is interpreted. In addition, there is likely a reporting bias, favoring positive results, especially in asTGA/ccTGA groups, but it is impossible to ascertain whether this is due to negative results not being reported or strong effects being always observed.

CONCLUSION

This systematic review and meta-analysis showed that STE measurements were associated with outcomes in a variety of CHDs such as RV strain in asTGA/ccTGA, biventricular strain in ToF, and LV strain in cAS/BAV, with potential for added value over conventional imaging and clinical parameters. In SV palliation, ventricular strain and strain rate were associated with outcomes when measured at any surgical stage, except for before the Norwood operation. Therefore, clinical use of STE in CHD should be encouraged and improving the quality of the evidence available made a priority, to allow for future disease-specific recommendations to be improved.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

CONFLICTS OF INTEREST

None.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.echo.2023.11.003.

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