Domains and outcome measures for the assessment of cardiac involvement in juvenile and adult systemic sclerosis: a scoping literature review

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Supplementary Table S1. Applicability of cardiac outcome measures in systemic sclerosis.

Outcome measures	Strengths	Limitations	Feasibility	Paediatric applicability
Electrocardiogram (ECG)				
Standard ECG	Widely available, non-invasive assessment of electrical abnormalities; may detect conduction abnormalities, arrhythmias, and repolarisation changes associated with cardiac involvement. Recommended yearly for cardiac screening in aSSc	Limited sensitivity for subclinical cardiac involvement; abnormalities are often non-specific.	Facilitators: Acquisition time <5 minutes. No consumables beyond disposable electrodes. Interpretable without subspecialty expertise. Easily integrated into routine clinic visits. Minimal standardisation burden for multicentre protocols. Barriers: None significant.	Used in all 3 paediatric jSSc studies. Well-established paediatric normative values with age-specific interpretation criteria (QTc, axis, voltage) and easily applicable to jSSc patients. Tolerated across all age groups including infants. Recommended for cardiac screening in jSSc
24-H Holter monitoring	Non-invasive detection of intermittent arrhythmias and conduction abnormalities.	Limited sensitivity for myocardial structural abnormalities and subclinical involvement.	Facilitators: Can be initiated during a clinic visit. Newer patch-based monitors extend monitoring to 14 days with improved comfort. Barriers: Requires 24–72 hours of continuous wear. Return visit or mailing needed for device retrieval. Analysis requires dedicated software and technician time for arrhythmia adjudication. Device variability across sites adds logistical burden for multicentre studies.	Used in all 3 paediatric jSSc studies. Compliance may be limited in young children (<5 years) who may not tolerate leads/wires for prolonged periods; adhesive patch monitors improve tolerability. Paediatric arrhythmia reference ranges and age-specific heart rate norms available. Caregiver involvement required for younger children.

P-QRS-T dispersion	Non-invasive assessment of repolarisation abnormalities and potential arrhythmic risk	Limited standardisation, use mostly as research tool. Uncertain clinical relevance in SSc.	Facilitators: Derived from standard 12-lead ECG; no additional equipment needed. Barriers: Requires manual or semi-automated measurement of intervals across all leads, adding analysis time. No standardised measurement protocol; high inter-reader variability. Limited evidence base in SSc	Not evaluated in any paediatric jSSc study. Paediatric normative values for QT dispersion published but limited; P-wave and QRS dispersion norms in children are sparse. Not included in jSSc recommendations. Clinical significance in jSSc unknown
Standard echocardiogram				
Left ventricular ejection fraction (LFEV)	Widely used assessment of global myocardial performance	Limited sensitivity for subclinical dysfunction	Facilitators: Routinely acquired during any standard echocardiogram. Biplane Simpson's method widely standardised (ASE). Same-day results. Barriers: Requires trained sonographer for acquisition and cardiologist for interpretation. Image quality dependent on acoustic windows and body habitus. Geometric assumptions may reduce accuracy in remodelled ventricles.	Used in all 3 paediatric jSSc studies. Included in J4S severity score and jSSc recommendations. Comprehensive paediatric z-score databases available. Acoustic windows generally superior in children. No sedation typically required in cooperative children (>3 years).
LV diastolic function	May identify early myocardial involvement before overt systolic impairment	Load-dependent assessment	Facilitators: Acquired during standard echocardiography session (no additional patient time). Standardised grading criteria available (ASE/EACVI). Barriers: Multiple parameters required for grading (E/A ratio, E/e', LAVI, TR velocity); interpretation complexity higher than LVEF. Heart rate and loading conditions affect measurements.	Used in all 3 paediatric jSSc studies. Paediatric diastolic function assessment feasible but interpretation differs from adults, with great variability in pre-adolescents. Validation studies for paediatric age are lacking. Not currently included in jSSc recommendations.
RV systolic function	Provides information on right ventricular involvement, particularly in the context of pulmonary vascular disease	Limited accuracy due to the complex RV geometry	Facilitators: TAPSE and FAC obtainable during standard echocardiography. TAPSE is a	Used in all 3 paediatric jSSc studies. Paediatric z-scores for TAPSE available and age-indexed. RV assessment

			simple, reproducible single-measurement parameter. Barriers: RV geometry is complex; no single parameter fully captures RV function. Multiple complementary measures often needed (TAPSE, FAC, S')	particularly relevant given the higher cardiac risk in certain jSSc subsets (*e.g.*, sine scleroderma jSSc). Not currently included in jSSc recommendations despite potential relevance
Valve function	Detection of structural valve abnormalities and associated hemodynamic consequences	Valve disease is relatively uncommon and not specific for SSc-related cardiac involvement	Facilitators: Routinely assessed during any standard echocardiogram. Standardised grading criteria (ASE) widely adopted. Barriers: Tricuspid regurgitation velocity (used for estimated PAP) may be absent or uninterpretable in a proportion of patients. Valvular assessment adds minimal incremental time.	Feasible across all paediatric age groups. Paediatric valve assessment well established with age-specific normative data. Seldom assessed as a specific outcome measure in SSc studies (adult or paediatric). Clinical relevance as a standalone cardiac outcome measure in jSSc is uncertain
sPAP	Essential non-invasive screening tool for pulmonary hypertension, routinely assessed in aSSc	Abnormal findings require confirmation by right heart catheterisation	Facilitators: Derived from tricuspid regurgitation velocity during standard echocardiography; no additional equipment. Non-invasive surrogate for pulmonary hemodynamics. Barriers: Requires measurable tricuspid regurgitation jet (absent in a proportion of patients). Tends to overestimate or underestimate PAP compared with RHC. Accuracy affected by right atrial pressure estimation	Used in all 3 paediatric jSSc studies. Included in jSSc recommendations. Paediatric echocardiographic estimation of sPAP follows the same principles as in adults. Lower prevalence of PAH in jSSc compared with adult SSc may reduce the frequency of abnormal findings. Correlation with RHC not validated specifically in jSSc
Pericardial effusion	Simple and reproducible detection of pericardial involvement; may reflect cardiac involvement or disease activity.	Clinical significance depends on severity and associated findings	Facilitators: Identified during any standard echocardiogram with no additional acquisition time. Qualitative assessment (absent/small/moderate/large) is straightforward and reproducible. Barriers: Quantification methods	Feasible across all paediatric age groups. Pericardial disease is among the most common cardiac manifestations in jSSc. Detection is straightforward but longitudinal use as a quantitative outcome measure is

			vary across studies. Small effusions may be physiological and of uncertain clinical significance.	limited by lack of standardised grading specific to SSc
Advanced echocardiogram - Speckle-tracking echocardiography (STE)				
LV global longitudinal strain (LV-GLS)	Potential to identify subclinical LV myocardial dysfunction despite normal LVEF in aSSc	Lower availability than conventional echocardiography. Specialised equipment and dedicated software required. Experienced operators required. Limited standardisation in SSc.	Facilitators: Can be acquired during the same session as standard echocardiography (no additional patient time). Most widely studied and reproducible strain parameter. Barriers: Requires post-processing with vendor-specific software (10–15 minutes). Dedicated training needed beyond standard echocardiography competency. Multicentre comparability requires single-vendor standardisation or vendor-neutral platforms.	Used in 1 paediatric jSSc study. Paediatric normative values published but limited by small sample sizes and inter-vendor variability; robust z-scores not yet established. ASE paediatric guidelines support use alongside conventional measures in specific contexts (*e.g*. cardio-oncology). Requires paediatric-specific validation in jSSc.
RV strain	Potential for early detection of subclinical RV dysfunction, particularly in SSc-associated PAH.	Lower availability than conventional echocardiography. Specialised equipment and dedicated software required. Experienced operators required. Limited standardisation in SSc.	Facilitators: Acquired simultaneously with LV-GLS during the same STE session. Provides quantitative assessment of RV function beyond TAPSE. Barriers: RV free-wall strain measurement is technically more challenging than LV-GLS due to RV geometry and thin wall. Less standardised than LV-GLS; higher measurement variability.	Not specifically evaluated as a standalone parameter in paediatric jSSc studies. Paediatric normative data for RV strain more limited than for LV-GLS. Potentially relevant given the importance of RV function in PAH-related cardiac involvement, but requires validation in jSSc
3D/4D parameters	More accurate assessment of ventricular volumes and function, compared with 2D echocardiography.	Lower availability than conventional echocardiography. Specialised equipment and dedicated software required. Experienced operators required. Limited data in SSc.	Facilitators: Provides volumetric assessment without geometric assumptions. Barriers: Requires dedicated 3D transducer and specialised analysis software. Longer acquisition and post-processing time than 2D STE. Limited availability even in tertiary centres. Highly operator-dependent; steep learning curve.	Feasible in experienced paediatric centres, but paediatric SSc-specific evidence is lacking. Not evaluated in any paediatric jSSc study. Paediatric 3D echocardiographic normative data exist primarily for congenital heart disease, not for acquired myocardial disease.

				Very limited evidence base; premature for consideration as a jSSc outcome measure.
Cardiac magnetic resonance imaging (cMRI)				
Systolic function	Objective and highly reproducible assessment of biventricular systolic function and ventricular volumes.	Limited sensitivity for early myocardial involvement, as systolic function is often preserved in SSs. Limited availability compared with echocardiography.	Facilitators: cMRI is the reference standard for biventricular volumes and EF; directly measured without geometric assumptions. Highly reproducible, reducing sample sizes needed for longitudinal studies. Barriers: Acquisition time 30-60 minutes; patient must remain still. Scheduling constraints due to limited scanner availability. Requires dedicated cMRI-trained physician for interpretation. Results typically not in the same day	Not evaluated in any paediatric jSSc study. Sedation or general anaesthesia frequently required in children <7-8 years, limiting serial use. SCMR paediatric consensus supports use for acquired heart disease in children. Paediatric normative data for volumes/function available but not validated in jSSc.
Speckle tracking MRI	Detects subclinical LV and RV myocardial dysfunction despite preserved LVEF. Potential diagnostic/prognostic value in aSSc	Dedicated software required. Limited evidence and need for further validation in SSc.	Facilitators: Feature-tracking can be performed on standard cine images without additional acquisition sequences. Barriers: Requires specialised post-processing software. Less validated than echocardiographic STE. No standardised protocols; high inter-software variability. Very limited evidence base in SSc.	Not evaluated in any paediatric jSSc study. Paediatric feature-tracking MRI data extremely limited. No paediatric normative values established for SSc-relevant parameters. Premature for consideration as a jSSc outcome measure.
Tissue characterisation (LGE - T1/T2 mapping)	Early detection of SSc-related myocardial inflammation and fibrosis, potentially identifying subclinical cardiac involvement.	Limited evidence on quantitative parameters and prognostic thresholds in aSSc.	Facilitators: Uniquely identifies myocardial fibrosis (LGE) and diffuse myocardial disease (T1/T2 mapping) non-invasively. Provides information not obtainable by any other outcome measure. Barriers: LGE requires gadolinium contrast (renal function screening needed). T1/T2 mapping sequences require site-specific calibration; values vary across scanners and	Not evaluated in any paediatric jSSc study. Gadolinium dosing follows weight-based paediatric protocols; linear agents avoided in young children per current recommendations. Paediatric T1/T2 mapping normative values emerging but scanner-specific. Sedation requirements in young children further limit

			field strengths. Harmonised protocols needed for multicentre comparability.	serial use for tissue characterisation
Pulmonary arterial pressure (cMRI-derived)	Can provide non-invasive assessment of pulmonary vascular and right heart changes associated with pulmonary hypertension	Indirect assessment of pulmonary pressures. Limited evidence in SSc	Facilitators: Non-invasive alternative to RHC for estimating pulmonary hemodynamic. Barriers: Multiple indirect methods exist (interventricular septal curvature, PA flow patterns); none validated as RHC substitutes. Very limited evidence base in SSc. Not standardised across centres.	Not evaluated in any paediatric jSSc study. Paediatric data on cMRI-derived PAP estimation extremely limited. Not validated against RHC in paediatric SSc populations. Premature for consideration as a jSSc outcome measure.
Cardiac stress tests				
Standard exercise testing	Provides a simple assessment of exercise tolerance and functional capacity. May reveal exercise-induced symptoms or abnormal cardiovascular response not evident at rest.	Exercise performance is influenced also by pulmonary, and musculoskeletal co-factors, limiting cardiac specificity. Dependent on patient motivation and protocol used.	Facilitators: Requires treadmill or cycle ergometer and standard ECG monitoring; widely available. Session duration 15–20 minutes. Barriers: Requires patient cooperation and adequate exercise capacity. Protocols vary (Bruce, modified Bruce); standardisation needed for multicentre use.	Not evaluated in any paediatric jSSc study. Feasible in children ≥6–8 years who can follow exercise instructions. Paediatric-specific protocols (*e.g.,* modified Bruce) and normative values available. Limited relevance as a standalone cardiac outcome measure in jSSc given sparse evidence.
Cardiopulmonary exercise testing (CPET)	Objective and comprehensive assessment of cardiopulmonary exercise capacity	Exercise performance is influenced also by pulmonary, and musculoskeletal co-factors, limiting cardiac specificity. Requires specialised equipment and expertise.	Facilitators: Provides objective, quantitative assessment of integrated cardiopulmonary function (peak VO_2, VE/VCO_2 slope). Barriers: Requires metabolic cart, calibrated ergometer, and trained exercise physiologist; session duration 30-45 minutes. Equipment not universally available. Effort-dependent; learning effect may affect serial measurements.	Not evaluated in any paediatric jSSc study. Requires developmental maturity (typically ≥8–10 years). Paediatric normative values for peak VO_2 and ventilatory parameters available (height- and age-adjusted). No jSSc-specific paediatric data exist. Cooperation and motivation may limit reliability in younger children.
6-minute walk test (6MWT)	Objective, simple, and reproducible measure of functional capacity. Widely	Affected by pulmonary and musculoskeletal involvement	Facilitators: Requires only a flat 30-meter corridor, stopwatch, and pulse oximeter. Completed in <10	Not evaluated in any paediatric jSSc study for cardiac assessment. Included in jSSc

	used in pulmonary hypertension and cardiopulmonary disease monitoring in aSSc.	and by demographic factors, limiting cardiac specificity.	minutes. No specialised personnel needed for administration. Simple to standardise across sites (ATS protocol). Barriers: Effort-dependent; influenced by motivation, musculoskeletal limitations, and deconditioning. Learning effect may affect serial measurements. Non-specific (reflects cardiopulmonary and musculoskeletal function)	recommendations for pulmonary assessment (not cardiac-specific). Paediatric reference values and prediction equations available for ages 6-18 years. Reliability limited in children <6 years due to cooperation and comprehension requirements. Role as a cardiac-specific outcome measure in jSSc requires clarification.
cMRI stress test	Assesses myocardial perfusion and microvascular dysfunction in response to stress, complemented by tissue characterisation, possibly providing additional information beyond resting cMRI in adult SSc.	Limited availability, costly, need for specialised expertise, need for contrast and pharmacological stress	Facilitators: Combines functional stress assessment with tissue characterisation in a single session. Barriers: Requires pharmacological stress agents (adenosine/dobutamine) in addition to standard cMRI infrastructure. Longer scan time than resting cMRI. Requires experienced cMRI team for stress protocol supervision. Very limited evidence base in SSc	Not evaluated in any paediatric jSSc study. Pharmacological stress cMRI feasible in children but requires paediatric anaesthesia/sedation support and experienced team. Very limited paediatric data outside congenital heart disease. Premature for consideration as a jSSc outcome measure.
Cardiac biomarkers				
NT-proBNP	Biomarker of myocardial stress; incorporated into the PAH screening algorithms, recommended for annual cardiac screening in aSSc	Limited cardiac specificity; influenced by age, renal function, and other conditions such as heart failure.	Facilitators: Standard venipuncture; can be added to routine blood draws without additional patient burden. Results available within hours using automated platforms. Assay standardisation across manufacturers well established, facilitating multicentre comparability. Barriers: None significant beyond standard venipuncture requirements.	Used in 1 paediatric jSSc study. Included in jSSc research agenda. Paediatric reference values strongly age-dependent: markedly elevated in neonates (up to 10× adult values), declining through childhood with stabilisation by adolescence. Age-specific cut-offs published. Venipuncture well tolerated in school-age children; may require

				procedural support in younger children.
Troponin	Biomarker of myocardial injury; recommended for annual cardiac screening in aSSc and may help detect subclinical myocardial involvement.	Limited specificity for SSc-related myocardial injury. Influenced by renal function, age, hemodynamic stress, and other causes of myocardial injury.	Facilitators: Standard venipuncture; same logistical advantages as NT-proBNP. High-sensitivity assays widely available on automated platforms. Barriers: None significant beyond standard venipuncture requirements.	Not evaluated in any paediatric jSSc study. High-sensitivity assays detect values in most children, but age- and sex-specific 99th percentile upper reference limits differ from adults. Paediatric-specific cut-offs published. Role as a longitudinal outcome measure for myocardial injury in jSSc is undefined
Right heart catheterisation (RHC)	Gold standard for the diagnosis and characterisation of pulmonary hypertension; provides direct measurements of pulmonary pressures and vascular resistance and allows disease classification.	Invasive procedure requiring specialised expertise; associated with procedural risks; not suitable for routine screening.	Facilitators: Directly measured hemodynamic data (mPAP, PAWP, PVR, cardiac output). Objective and quantitative; facilitates cross-centre comparability when standardised zeroing and measurement protocols are used. Gold standard for PAH diagnosis. Barriers: Requires catheterisation laboratory, fluoroscopy, and procedural sedation/anaesthesia. Minimum half-day procedure including recovery. Should be performed only at centres with experienced interventional teams. Not suitable for routine serial monitoring due to procedural burden.	Not used in any paediatric jSSc study. Included in jSSc research agenda but not in routine recommendations. Gold standard for PAH diagnosis in children per AHA/ATS and ESC/ERS paediatric PH guidelines. Complication rate 1-3% in paediatric PAH registries; requires experienced paediatric interventional team. General anaesthesia typically required in young children. Lower prevalence of PAH in jSSc compared with adult SSc may limit the frequency of clinical indication.

This Table provides a qualitative summary based on the findings of the present scoping review and informed by current guidelines and recommendations for cardiac assessment in adult and juvenile SSc (1-3). Paediatric feasibility and applicability considerations are informed by published paediatric cardiology guidelines and reference standards (4-7). This summary is intended to support the subsequent IJOG consensus process and does not constitute a formal assessment of measurement performance.
aSSc: adult-onset systemic sclerosis; ASE: American Society of Echocardiography; ATS: American Thoracic Society; E/A: ratio of early to late mitral inflow velocities; E/e': ratio of early mitral inflow velocity to early diastolic mitral annular velocity; EACVI: European Association of Cardiovascular Imaging; ESC/ERS: European Society of Cardiology/European Respiratory Society; FAC: fractional area change; IJOG: International Juvenile Systemic Sclerosis Outcome Group; J4S: Juvenile Systemic Sclerosis Severity Score; jSSc: juvenile systemic sclerosis; LAVI: left atrial volume index; LGE: late gadolinium enhancement; LV: left ventricle; mPAP: mean pulmonary arterial

pressure; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PA: pulmonary artery; PAH: pulmonary arterial hypertension; PAP: pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; RHC: right heart catheterisation; RV: right ventricle; S': systolic tricuspid annular velocity; SCMR: Society for Cardiovascular Magnetic Resonance; sPAP: systolic pulmonary arterial pressure; SSc: systemic sclerosis; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation; VE/VCO_2: ventilatory equivalent for carbon dioxide; VO_2: oxygen consumption.

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