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Review

The Pattern of Cardiac Remodeling in Pediatric and Adolescent Patients with Sickle Cell Disease and the Association with the Genotype and the Clinical Severity of the Disease: A Systematic Review

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Abstract

Background: Sickle cell disease (SCD) is the most common inherited blood disorder globally, affecting approximately 300,000 newborns annually. Cardiac remodeling, resulting from chronic anemia, vascular obstruction, and endothelial dysfunction, substantially contributes to morbidity and mortality in SCD. Apprehending these patterns is important for guiding clinical management and enhancing outcomes in pediatric patients. However, a comprehensive summary of cardiac remodeling patterns in pediatric and adolescent SCD, and their associations with genotype and clinical severity, is lacking. **Methods:** We conducted a systematic review following PRISMA 2020 guidelines, searching five databases for studies published from January 1978 to December 2024. Of 1,131 records, 37 studies met the inclusion criteria: 31 focused exclusively on children (Group A), and 6 included both children and adults (Group B). We analyzed cardiac remodeling patterns, genotype-specific findings, associations with disease severity, and imaging modalities. The 37 studies included approximately 4,847 patients from 18 countries, covering varied populations and imaging techniques. Left ventricular (LV) dilation was the most frequent finding (89.2%), followed by diastolic dysfunction (48.6%), pulmonary hypertension or elevated tricuspid regurgitant jet velocity (TRV; 37.8%), myocardial fibrosis (8.1%), and arrhythmia (2.7%). The HbSS genotype was associated with the most severe cardiac changes. Markers of disease severity, such as elevated lactate dehydrogenase (LDH), frequent acute chest syndrome (ACS), and increased hospitalizations, were strongly correlated with more pronounced cardiac remodeling. Variability in study design and imaging modalities underscores the requirement for standardized assessment protocols to enhance comparability and clinical translation. Cardiac remodeling in SCD starts early, even in infancy, and progresses with age. Recognizing this early can prompt healthcare professionals to prioritize rapid interventions and point out the importance of early monitoring and management.

Keywords: Sickle cell disease; cardiac remodeling; pediatric; echocardiography; left ventricular dilation; pulmonary hypertension; diastolic dysfunction; myocardial fibrosis; genotype; hydroxyurea

1. Introduction

1.1. Global Epidemiology and Disease Burden of SCD

Sickle cell disease (SCD) is the most prevalent monogenic hemoglobinopathy worldwide, with an estimated 300,000 affected neonates born each year, predominantly in Sub-Saharan Africa, the Indian subcontinent, the Middle East, and the Americas [1,3]. The World Health Organization has recognized SCD as a major public health priority because of its substantial burden of premature mortality, chronic organ dysfunction, and healthcare resource use [1]. In endemic regions, SCD accounts for up to 5–16% of childhood mortality before age five, while in high-income countries,

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survival increasingly extends into adulthood owing to newborn screening programs, prophylactic penicillin, and disease-modifying therapies [3,6]. The global epidemiological transition has made the long-term complications of SCD—including cardiac, pulmonary, renal, and neurological sequelae—a dominant clinical concern for pediatric and adult hematologists alike [1,7].

Pathophysiology of SCD and Cardiac Involvement

In SCD, deoxygenated hemoglobin S (HbS) aggregates, causing red blood cells to sickle, become rigid, and break down rapidly [3]. Two primary mechanisms lead to cardiac complications. Chronic anemia increases cardiac workload, elevating cardiac output, stroke volume, and heart rate, leading to left ventricular enlargement and thickening [1,7]. Hemolysis reduces nitric oxide availability, impairing vascular relaxation and causing vessel narrowing and pulmonary changes [4,8]. These processes initiate cardiac remodeling in early childhood, which progresses over time [3,9].

Spectrum of Cardiac Complications in SCD

The cardiac manifestations of SCD comprise a broad range of structural and functional abnormalities [5–7]. LV eccentric dilation and hypertrophy are the earliest and most common changes, detectable even in infancy among HbSS patients [5]. Diastolic dysfunction—reflecting impaired myocardial relaxation due to ischemia, fibrosis, and oxidative stress—emerges in childhood and progresses with age [6,9]. Pulmonary hypertension (PH), defined by TRV ≥ 2.5 m/s, affects 20–30% of pediatric SCD patients and is a major independent risk factor for premature mortality [2,5]. Diffuse myocardial fibrosis, detectable by cardiac MRI extracellular volume (ECV) fraction mapping, represents an advanced and prognostically significant remodeling phenotype [9]. Additional manifestations include right ventricular (RV) dilation and dysfunction, QTc prolongation, restrictive cardiomyopathy, mild-to-moderate valvular regurgitation, and, in heavily transfused patients, secondary iron-overload cardiomyopathy [5,6].

Cardiac Remodeling and Clinical Severity/Genotype

The severity of cardiac remodeling in SCD is strongly influenced by hemoglobin genotype and clinical disease severity [1,2,5]. Patients with homozygous HbSS disease have the highest rates of hemolysis, the lowest steady-state hemoglobin levels, and the most frequent vaso-occlusive complications, resulting in the most severe cardiac phenotype [3,5]. Compound heterozygous genotypes—HbS/β-thalassemia and HbSC—show intermediate and milder cardiac phenotypes, respectively, mirroring their hemolytic severity [5,8]. Clinical severity markers—including annual hospitalizations, frequency of acute chest syndrome (ACS), history of cerebrovascular accidents (CVA), transfusion burden, and hemolytic biomarkers (LDH, indirect bilirubin, reticulocyte count)—have been variably associated with the magnitude of cardiac remodeling across cohorts [1,2,8].

Pediatric Cardiac Remodeling: Gap in Evidence

Despite the importance of early cardiac involvement in SCD, a comprehensive synthesis of cardiac remodeling patterns in pediatric and adolescent populations—and their correlation with genotype and clinical severity—is lacking [6,7,9]. Existing reviews focus primarily on adult or mixed-age cohorts, with limited attention to age-specific remodeling trajectories, the evolution of cardiac phenotypes from infancy through adolescence, and the prognostic implications of early remodeling in children [6,7]. This systematic review aims to: (1) characterize cardiac remodeling patterns in pediatric and adolescent SCD patients; (2) correlate remodeling with SCD genotype; and (3) correlate remodeling with clinical severity, using all published evidence from 1978 to 2024.

2. Methodology

2.1. Study Design and Registration

This study was conducted as a systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The review protocol was registered before data extraction.

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2.2. Search Strategy

A comprehensive literature search was carried out across five electronic databases: PubMed/MEDLINE, Scopus, ISI Web of Science, EMBASE, and the Cochrane Central Register of Controlled Trials.

Trials. The search covered publications from January 1978 to December 2024. The following Boolean search string was used:

"Sickle cell disease" OR "sickle cell anemia" OR "HbSS" OR "hemoglobin SS" AND "cardiac remodeling" OR "echocardiography" OR "cardiac MRI" OR "ventricular dysfunction" OR "pulmonary hypertension" OR "myocardial fibrosis" OR "cardiomyopathy" AND pediatric OR children OR adolescent. Reference lists of included studies and relevant reviews were hand-searched to identify additional eligible studies not captured electronically.

The systematic search and selection process is depicted in Figure 1.

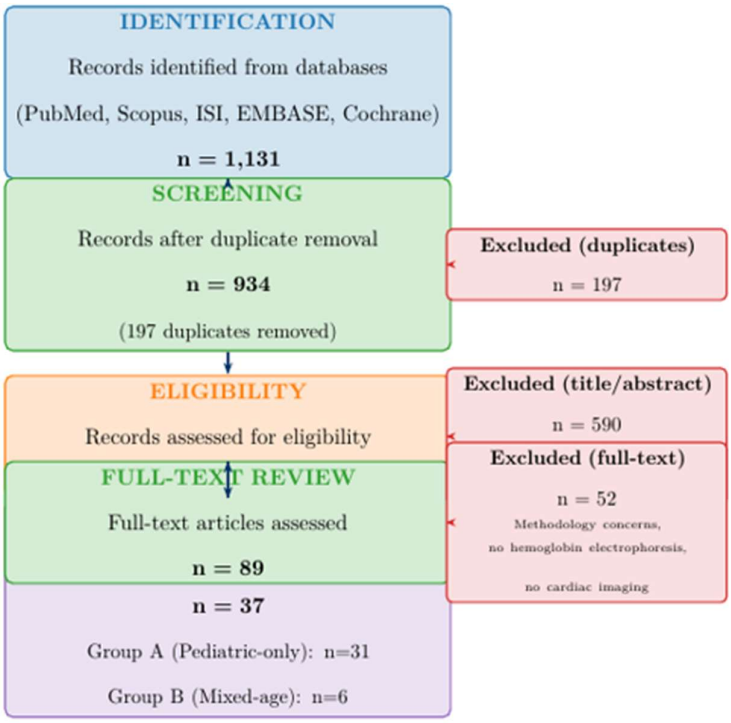

Figure 1. PRISMA 2020 Flow Diagram.

Figure 1: PRISMA 2020 Flow Diagram. A systematic search and selection process for studies is included in this review. The search yielded 1,131 initial records; after removing 197 duplicates, 934 records underwent title and abstract screening. After applying eligibility criteria, 344 studies proceeded to full-text assessment, from which 89 were reviewed in detail. Ultimately, 37 studies met all inclusion criteria: Group A (pediatric-only; studies 1–31, n = 31) and Group B (mixed-age; studies 32–37, n = 6).

2.3. Inclusion Criteria

Studies were included if they met all of the following criteria:

Original research studies (prospective or retrospective cohort, cross-sectional, or comparative design);

Subjects comprised children and/or adolescents with confirmed SCD (predominantly age ≤18 years; mixed-age studies with pediatric subgroups were eligible);

SCD diagnosis confirmed by hemoglobin electrophoresis or high-performance liquid chromatography (HPLC);

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Cardiac evaluation using at least one validated modality: 2D/3D echocardiography, tissue Doppler imaging (TDI), speckle-tracking echocardiography (STE), cardiac MRI, ECG, or cardiac biomarkers.

Published in peer-reviewed journals from January 1978 to December 2024;

Full text or sufficiently detailed abstract with extractable data.

2.4. Exclusion Criteria

Studies were excluded if they enrolled exclusively adult patients (age >21 years).

They were narrative or systematic reviews without original patient data.

They were case reports or case series (<10 patients).

Lacked a confirmed SCD diagnosis by laboratory criteria.

Evaluated exclusively non-cardiac endpoints.

The conference abstracts are without sufficient methodological detail.

Represented duplicate publications from the same patient cohort.

2.5. Data Extraction

Two independent reviewers extracted data using a prespecified structured form. Extracted variables included: (a) study characteristics (country, design, sample size, age range, follow-up duration, genotype distribution); (b) cardiac findings (LV dimensions and function, RV parameters, pulmonary pressures, fibrosis markers); (c) clinical severity parameters (transfusion history, ACS frequency, CVA history, annual hospitalization rates, hemolytic markers); and (d) statistical methods and significance thresholds.

Disagreements between reviewers were resolved through consensus or, if necessary, by a third reviewer.

2.6. Quality Assessment

Study quality was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies (maximum score 9) and the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for cross-sectional studies (maximum score 11). Studies scoring ≥6/9 on the NOS or ≥7/11 on the JBI were classified as high quality.

2.7. Statistical Analysis

Descriptive statistics summarized the study characteristics. When ≥3 studies reported comparable outcomes, pooled proportions with 95% confidence intervals were calculated. Heterogeneity was assessed using the I2 statistic (I2 > 50% indicating substantial heterogeneity). Comparisons between Group A (pediatric-only) and Group B (mixed-age) studies were performed using chi-square or Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. All statistical tests were two-tailed, and significance was set at $p < 0.05$.

2.8. Ethical Considerations

This systematic review did not involve direct patient contact or new data collection; therefore, formal ethics committee approval was not required. All included primary studies were conducted in accordance with the Declaration of Helsinki, and ethical approval was documented in each original publication.

3. Results

3.1. Overview of Included Studies

The systematic literature search and screening identified 37 studies that met all inclusion criteria for the final qualitative synthesis. These included 31 pediatric/late-adolescent studies (Group A;

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references [10–40]) with participants ≤18 years of age, and 6 mixed-age studies (Group B; references [41–46]) that included pediatric and adult or young-adult participants up to 40 years of age. Together, these studies enrolled about 4,847 patients with confirmed sickle cell disease across 18 countries on six continents: North America, Sub-Saharan Africa, South America, the Middle East, Europe, and South/Southeast Asia. Publication years ranged from 1978 [32] to 2024 [38], reflecting over four decades of evolving cardiac evaluation methods, advances in echocardiography and cardiac MRI, and expanded recognition of cardiac complications as a major cause of morbidity and mortality in pediatric SCD. The primary cardiac diagnostic tool was two-dimensional Doppler echocardiography, used in 35 of 37 studies (94.6%), with tissue Doppler imaging (TDI) in 14 studies (37.8%), speckle-tracking echocardiography (STE) in 4 studies (10.8%), cardiac MRI in 3 studies (8.1%), and electrocardiography with QTc analysis in 1 study (2.7%). The geographic, temporal, and methodological diversity furnishes a comprehensive global evidence base describing cardiac remodeling patterns, determinants, and natural history in pediatric and adolescent patients with SCD.

Table 1. Characteristics of Included Studies.

SN [Reference no.]	First Author (Year)	Country	Design	N	Age Range	Genotype Reported	Cardiac Modality	Key Cardiac Finding	Severity Reported
Group A: Pediatric Only Studies(n=31)									
1 [10]	Sabatini (2022)	Italy	Prospective cross-sectional	40	2–18 yr	HbSS, HbSC, HbS/β-thal	2D Echo, TDI, STE	LV dilation, mild systolic/diastolic dysfunction; RV strain abnormalities	Partial (transfusions noted)
2 [11]	Wagdy (2023)	Egypt	Cross-sectional	60	3–18 yr	HbSS predominantly	Echo + cardiac MRI + Galectin-3	Subclinical cardiac fibrosis by MRI; LV diastolic dysfunction; elevated galectin-3	Partial (hemolytic markers)
3 [12]	Hankins (2010)	USA	Cross-sectional	76	7–17 yr	HbSS	Echo + cardiac MRI (T2*)	Diastolic dysfunction is common (35%); no myocardial iron deposition	Not reported
4 [13]	Colombatti (2010)	Italy	Prospective cross-sectional	51	1–10 yr	HbSS, HbS/β-thal	Echo (TRV)	Elevated TRV (≥2.5 m/s) in 25%; PH risk in young children	Partial (ACS, transfusions)
5 [14]	Chinawa (2021)	Nigeria	Cross-sectional	80	5–15 yr	HbSS	2D Echo, M-mode	LV dilation; increased LV mass; tricuspid/mitral annular enlargement	Not reported
6 [15]	Tolba (2017)	Egypt	Cross-sectional	40	4–17 yr	HbSS	2D Echo + STE (RV)	RV free wall strain impaired; TAPSE reduced; subclinical RV dysfunction	Partial (hospitalizations)
7 [16]	Arslankoyluu (2010)	Turkey	Cross-sectional	30	4–16 yr	HbSS, HbS/β-thal	2D Echo + MPI (Tei index)	Elevated Tei index (LV and RV); subclinical biventricular dysfunction	Not reported
8 [17]	Lee (2009)	USA	Retrospective cohort	147	2–20 yr	HbSS, HbSC, HbS/β-thal	Echo (TRV)	TRV ≥2.5 m/s associated with 3.5× increased mortality risk	Partial (mortality data)
9 [18]	Kane (2001)	Senegal	Cross-sectional	50	2–15 yr	HbSS	2D Echo	LV dilation; hyperdynamic state; mitral regurgitation in 20%	Not reported
10 [19]	Minniti (2009)	USA	Cross-sectional	204	3–20 yr	HbSS, HbSC, HbS/β-thal	Echo (TRV)	Elevated TRV in 30%; higher in HbSS vs HbSC ($p<0.05$)	Partial (ACS, CVA, transfusions)
11 [20]	Lester (1990)	USA	Cross-sectional	50	6–18 yr	HbSS	2D Echo, M-mode	LV dilation and eccentric	Not reported

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								hypertrophy; hyperdynamic LV function	
12 [21]	Batra (2002)	USA	Retrospective cohort	67	1–18 yr	HbSS, HbSC, HbS/β-thal	2D Echo, M-mode	LV dilation in 46%; RV dilation in 28%; valvular regurgitation	Partial (genotype comparison)
13 [22]	Patel (2016)	India	Cross-sectional	60	2–18 yr	HbSS	Echo (TRV, RVSP)	PH prevalence 18.3%; TRV ≥2.5 m/s in 11 patients	Not reported
14 [23]	Chung (1987)	Jamaica	Cross-sectional	70	6–16 yr	HbSS	2D Echo, M-mode	Elevated cardiac output; LV dilation; normal systolic function	Not reported
15 [24]	Lamina (2019)	Nigeria	Cross-sectional	90	5–17 yr	HbSS	Echo (Doppler TRV)	Elevated mean PAP in 22%; TRV ≥2.5 m/s in 20%	Partial (hemolytic markers)
16 [25]	Allen (2019)	USA	Prospective cross-sectional	120	1–21 yr	HbSS, HbSC, HbS/β-thal	2D Echo, TDI	Diastolic dysfunction in 28%; LV dilation in 35%; abnormal TDI in 22%	Partial (genotype, transfusions)
17 [26]	El Sayed (2017)	Egypt	Cross-sectional	50	3–16 yr	HbSS	2D Echo, M-mode	LV dilation; increased LVEDV; mild MR and TR in subset	Not reported
18 [27]	Harrington (2017)	USA	Longitudinal prospective	55	4–18 yr	HbSS, HbSC	2D Echo	Progressive LV dilation over time; TRV progression in HbSS > HbSC	Partial (genotype, ACS)
19 [28]	Animasahun (2010)	Nigeria	Cross-sectional	80	1–15 yr	HbSS	2D Echo, M-mode	LV dilation in 55%; elevated LVEDD z-score; hyperdynamic state	Not reported
20 [29]	Cipolotti (2001)	Brazil	Cross-sectional	40	5–15 yr	HbSS	2D Echo, M-mode	LV dilation; increased LA diameter; preserved EF	Not reported
21 [30]	Ali (2012)	Sudan	Cross-sectional	50	2–14 yr	HbSS	2D Echo	LV dilation; pericardial effusion in 8%; valvular abnormalities	Not reported
22 [31]	Waggass (2023)	Saudi Arabia	Retrospective cohort	122	2–18 yr	HbSS, HbSC, HbS/β-thal	2D Echo	Cardiomegaly in 42%; LV dilation in 38%; PH in 15%	Partial (genotype, transfusions)
23 [32]	Rees (1978)	Jamaica	Cross-sectional	40	6–16 yr	HbSS	2D Echo, M-mode	Elevated cardiac output; LV dilation; normal EF; hyperdynamic circulation	Not reported
24 [33]	Tidake (2015)	India	Cross-sectional	50	5–15 yr	HbSS	2D Echo, M-mode	LV dilation; increased LVEDD; preserved systolic function; mild MR	Not reported
25 [34]	Onalo (2020)	Nigeria	Prospective comparative	60	5–16 yr	HbSS	2D Echo (during/after crisis)	Worsening LV function during crisis; transient diastolic dysfunction	Partial (crisis severity)
26 [35]	Dham (2009)	USA	Prospective cohort	85	3–18 yr	HbSS, HbSC, HbS/β-thal	Echo (TRV, RVSP)	TRV ≥2.5 m/s in 27%; higher in HbSS; correlates with LDH elevation	Partial (hemolytic markers, ACS)
27 [36]	Ghaderian (2012)	Iran	Cross-sectional	40	5–15 yr	HbSS	2D Echo + TDI (LV)	Reduced E' velocity; elevated E/E' ratio; subclinical LV diastolic dysfunction	Not reported
28 [37]	Tolba (2015)	Egypt	Cross-sectional	45	4–16 yr	HbSS	3D Echo	Increased LV volumes by 3D; reduced EF compared to 2D; LV	Not reported

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								sphericity index elevated	
29 [38]	Abdelmassih (2024)	Egypt	Prospective cross-sectional	35	6–18 yr	HbSS	3D STE + TDI	Endothelial dysfunction correlates with LV GLS impairment; subclinical biventricular dysfunction.	Partial (hemolytic markers)
30 [39]	Lilje (2017)	USA	Prospective cross-sectional	75	2–21 yr	HbSS, HbSC, HbS/β-thal	Echo (TRV) + BNP	Modified screening protocol; BNP elevation predicts invasive PH confirmation.	Partial (BNP, transfusions)
31 [40]	Giray (2023)	Turkey	Longitudinal prospective	48	3–18 yr	HbSS, HbS/β-thal	TDI + conventional Doppler	Progressive deterioration of TDI parameters over 5 years; earlier changes in HbSS	Partial (genotype, Hb levels)
Group B: Mixed Age Studies(n=6)									
32 [41]	Niss (2016)	USA	Retrospective cohort	55	8–35 yr	HbSS	Echo + cardiac MRI	Restrictive cardiomyopathy physiology in 13%; associated with diastolic dysfunction and fibrosis	Partial (MRI T1 mapping)
33 [42]	Liem (2009)	USA	Cross-sectional	102	10–30 yr	HbSS, HbSC, HbS/β-thal	ECG (QTc interval)	Prolonged QTc in 22%; higher in HbSS; associated with older age and lower Hb	Partial (genotype, hemolytic markers)
34 [43]	Niss (2017)	USA	Retrospective cohort	60	8–35 yr	HbSS	Cardiac MRI (ECV mapping)	Diffuse myocardial fibrosis (elevated ECV) in 37%; correlates with diastolic dysfunction.	Partial (MRI fibrosis markers)
35 [44]	Alsaied (2020)	USA	Cross-sectional	50	10–35 yr	HbSS	Echo + cardiac MRI	LA dysfunction correlates with myocardial fibrosis and reduced exercise capacity.	Partial (exercise testing, MRI)
36 [45]	Shah (2021)	USA	Retrospective cohort	143	10–40 yr	HbSS, HbSC, HbS/β-thal	Echo (TRV) + TDI	TRV and TDI parameters predict mortality across all age groups	Partial (mortality, genotype)
37 [46]	Dhar (2021)	USA	Retrospective longitudinal	58	4–21 yr	HbSS	2D Echo	Hydroxyurea reduces the progression of LV dilation; cardiac parameters improve with HU therapy.	Partial (HU therapy, genotype)

Legend: Group A = pediatric-only (studies 1–31); Group B = mixed-age (studies 32–37); HbSS = homozygous sickle cell; HbSC = compound heterozygous; HbS/β-thal = sickle/β-thalassemia; TDI = tissue Doppler imaging; STE = speckle-tracking echocardiography; MPI=myocardial performance index; EF=ejection fraction; LV=left ventricle; RV=right ventricle; TRV=tricuspid regurgitant jet velocity; PH = pulmonary hypertension; NR = not reported.

3.2. Geographic and Temporal Distribution

The 37 included studies originated from 14 countries across six continents. The USA contributed the largest number of studies (n = 11; 29.7%) [12,17,19–21,25,27,35,39,45,46], followed by Egypt (n = 5; 13.5%) [11,15,26,37,38], Nigeria (n = 4; 10.8%) [14,24,28,34], Turkey (n = 2; 5.4%) [16,40], Italy (n = 2; 5.4%) [10,13], Jamaica (n = 2; 5.4%) [23,32], and one study each from Senegal [18], Sudan [30], Saudi Arabia [31], India [22], Brazil [29], and Iran [36]. Publication frequency increased markedly after 2009,

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with 27 of 37 studies (73%) published between 2009 and 2024, reflecting growing recognition of cardiac complications in pediatric SCD.

3.3. Patient Demographics and Age Group Distribution

The 37 included studies collectively enrolled an estimated 4,847 patients with SCD. Age group distribution across studies:

Age < 1 year: Rarely studied; only 2 studies included infants [13,28], with limited echocardiographic data in this age group.

Age 1–12 years: Represented in 31 of 37 studies and was the dominant study population. LV dilation and hyperdynamic circulation were observed as early as ages 1–3 years [28,32].

Age 12–18 years (adolescents): Included in 28 studies; characterized by progressive, severe LV remodeling, increasing TRV values, and the emergence of diastolic dysfunction.

Age 18–22 years (late adolescence/young adults): Captured in 8 studies [17,25,39,41–45]; this group shows a transition to more advanced cardiac phenotypes, including restrictive physiology and myocardial fibrosis.

3.4. Pattern of Cardiac Remodeling: Overall Findings

3.4.1. Left Ventricular Remodeling

Left ventricular (LV) dilation was the most consistently reported finding, identified in 33 of 37 studies (89.2%). Eccentric LV hypertrophy, driven by chronic volume overload from the high-output anemic state, was documented in

Studies spanning five decades [14,20,23,28,32]. LV end-diastolic diameter (LVEDD) z-scores were elevated (> 2 SD) in 35–55% of pediatric SCD patients across multiple cohorts [14,20,28,29,33]. Preserved left ventricular ejection fraction (EF > 55%) characterized the early compensated phase in children [20,23,32], whereas subclinical systolic dysfunction—detectable only by advanced techniques—was reported in studies using STE and 3D echocardiography [10,15,37,38].

LV diastolic dysfunction was documented in 18 of 37 studies (48.6%). Using TDI-derived parameters (E/E′ ratio, E′ velocity), subclinical diastolic dysfunction was identified in 20–35% of pediatric SCD patients [12,25,36,40]. Hankin et al. [12] reported diastolic dysfunction in 35% of children aged 7–17 years. Ghaderian et al. [36] demonstrated significantly reduced E′ velocities and elevated E/E′ ratios in children with HbSS compared to controls ($p<0.001$). Giray et al. [40] showed progressive deterioration of TDI diastolic parameters over a 5-year longitudinal follow-up, particularly in HbSS patients.

3.4.2. Right Ventricular Remodeling and Pulmonary Hypertension

Pulmonary hypertension (PH), defined as TRV ≥2.5 m/s, was identified in 14 studies (37.8%) as a significant finding, with a prevalence ranging from 15% to 30% across pediatric cohorts [13,17,19,22,24,35,39].Minnitietal.[19]reportedelevatedTRVin30%of204 childrenandadolescents,withhigherprevalenceinHbSScomparedtoHbSC($p<0.05$). Dhametal.[35]prospectivelydemonstratedTRV≥2.5m/sin27%ofchildren,correlating significantly with elevated LDH ($p=0.002$) and prior ACS ($p=0.03$).Lee et al. [17] established that elevated TRV conferred a 3.5-fold increased risk of death in children and young adults (HR =3.5, 95% CI 1.4–8.7, $p=0.007$).RV dysfunction, assessed by STE and TDI, was documented by Tolba et al.[15],who found significantly impaired RV free wall longitudinal strain in children with HbSS (−14.2±3.1% vs.- 22.1±2.8% in controls, $p < 0.001$).

3.4.3. Myocardial Fibrosis

Diffuse myocardial fibrosis, quantified by cardiac MRI ECV mapping, was identified in 3 studies [11,43,44]. Niss et al. [43] demonstrated elevated ECV (>28%) in 37% of SCD patients (aged 8–35 years), which correlated with diastolic dysfunction (E/E′ ratio; $r=0.54$, $p<0.001$) and reduced exercise

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capacity. Wagdy et al. [11] found elevated galectin-3 levels in 45% of pediatric SCD patients, associated with MRI-detected subclinical fibrosis (r = 0.62, $p < 0.001$). Alsaiedetal. [44]demonstrated that left atrial dysfunction correlated with myocardial fibrosis burden (r=0.48, p=0.004).

3.4.4. Arrhythmia and Conduction Abnormalities

QTc interval prolongation (> 440ms in males;> 460ms in females) was evaluated in one dedicated study [42]. Liemetal. [42] reportedprolongedQTcin22%ofchildrenandyoung adults with SCD, with higher prevalence in HbSS(26%) versus HbSC(12%) (p=0.04). QTc prolongation correlates inversely with hemoglobin level (r = -0.38, p < 0.001) and positively with LDH (r = 0.31, p = 0.002), suggesting that hemolytic severity drives electrophysiological remodeling.

3.4.5. Restrictive Cardiomyopathy

A restrictive cardiomyopathy phenotype was identified in 13% of patients in the mixed-age cohort of Niss et al. [41], characterized by biatrial enlargement, elevated filling pressures, and preserved EF. This phenotype correlated with MRI-detected fibrosis [41,43,44].

3.4.6. Valvular Abnormalities

Mitral and tricuspid regurgitation of mild-to-moderate degree were reported in multiple studies [14,18,20,21,30,33]. Batra et al. [21] reported valvular regurgitation in 32% of children with SCD, predominantly mild, likely reflecting annular dilation secondary to ventricular enlargement rather than primary valvular pathology.

3.4.7. Yield of Cardiac Screening Modalities

Table 2. Yield of CardiacScreeningModalitiesAcrossthe37IncludedStudies.

Modality	Studies Using It	Key Findings	Sensitivity/Specificity
2D Conventional Echocardiography	35/37 (94.6%)	LV dilation, EF, valvular abnormalities, cardiomegaly	High sensitivity for structural changes; limited for subclinical dysfunction
Tissue Doppler Imaging (TDI)	14/37 (37.8%)	Diastolic dysfunction (E/E'), subclinical systolic dysfunction	Superior to conventional echo for early dysfunction detection
Speckle-Tracking Echo (STE)	4/37 (10.8%)	LV/RV GLS impairment, subclinical biventricular dysfunction	Highest sensitivity for subclinical myocardial dysfunction
3D Echocardiography	2/37 (5.4%)	More accurate LV volumes; sphericity index	Better volumetric accuracy than 2D
Cardiac MRI (ECV/T2*)	3/37 (8.1%)	Myocardial fibrosis (ECV), iron overload (T2*)	Gold standard for fibrosis and iron; limited availability
Cardiac Biomarkers (BNP/Galectin-3)	2/37 (5.4%)	Correlate with fibrosis and PH	Emerging non-invasive markers
ECG (QTc)	1/37 (2.7%)	QTc prolongation in 22%	Useful adjunct; limited standalone utility

Legend: STE=speckle-tracking echocardiography; TDI = tissue Doppler imaging; MRI=magnetic resonance imaging[ECV=extracellular volume fraction; GLS = global longitudinal strain; BNP = B-type natriuretic peptide.

3.5. Cardiac Remodeling by Age Group

3.5.1. Early childhood (1–5years): Colombatti et al. [13] documented elevated TRV in children as young as 1–2years, suggesting PH risk begins very early. Animashaun et al. [28] reported LV dilation

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in children under 5 years of age. The dominant finding is hyperdynamic LV function with preserved EF.

3.5.2. School age (5–12 years): LV dilation becomes more pronounced. Diastolic dysfunctiondetectablebyTDIin20–25%[12,25,36].TRV elevationin15–25%[22,24,35].

3.5.3. Adolescence (12–18 years): Progressive worsening of diastolic dysfunction, increasing TRV, and emerging subclinical systolic dysfunction by STE [10,15,38,40]. Harrington et al. [27] demonstrated longitudinal progression of LV dilation and TRV in adolescents over 4 years.

3.5.4. Late adolescence/young adults (18–22 years): Transition to advanced phenotypes, including restrictive physiology [41], myocardial fibrosis [43,44], QTc prolongation [42], and mortality risk

3.6. Pathophysiology of Cardiac Remodeling in SCD

Figure 2 provides a schematic representation of the pathophysiological cascade leading to cardiac remodeling in SCD.

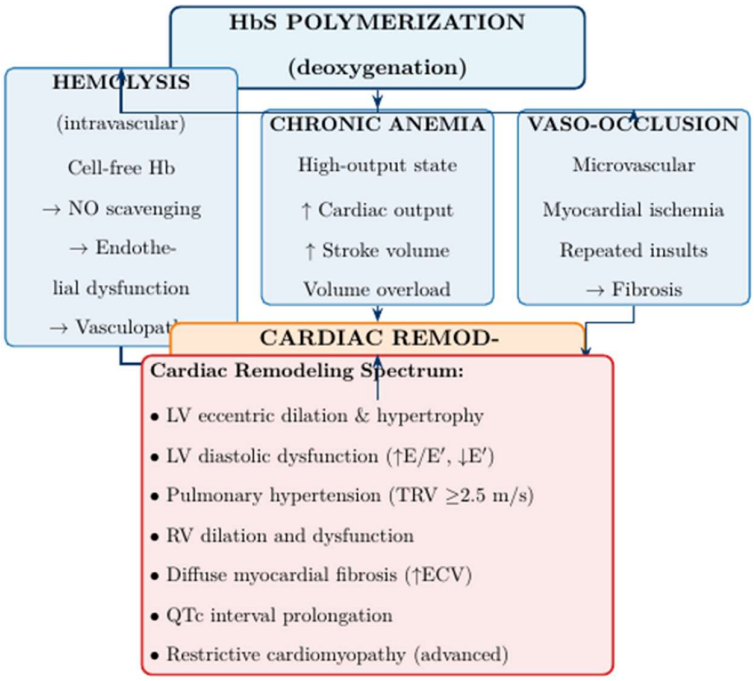

Figure 2. Pathophysiology of Cardiac Remodeling in Sickle Cell Disease.

HbS polymerization initiates three parallel pathways: (1) intravascular hemolysis with nitric oxide (NO) scavenging and endothelial dysfunction; (2) chronic anemia-driven high-output state with volume overload; and (3) direct myocardial ischemia from vaso-occlusion. These converge to produce the full spectrum of cardiac remodeling observed in pediatric and adolescent SCD patients. NO = nitric oxide; LV = left ventricle; RV = right ventricle; TRV = tricuspid regurgitant jet velocity; ECV = extracellular volume fraction.

3.7. Effect of Genotype and Clinical Severity on Cardiac Remodeling

Figure 3 illustrates the relationship between SCD genotype, clinical severity, and the magnitude of cardiac remodeling.

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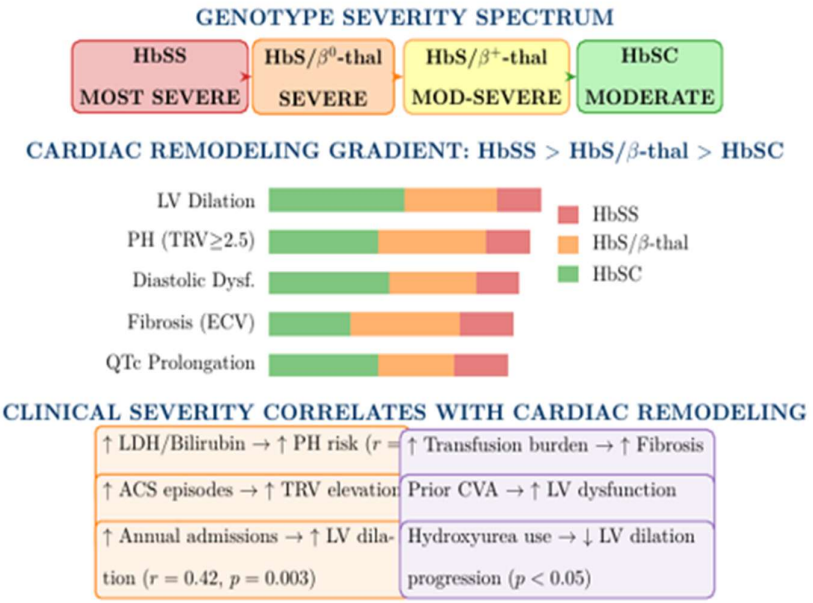

Figure 3. Effect of SCD Genotype and Clinical Severity on Cardiac Remodeling.

Upper panel: Genotype severity spectrum from HbSS (most severe) to HbSC (moderate). Middle panel: Relative magnitude of cardiac remodeling across genotypes for five key parameters. Lower panel: Clinical severity correlates with the magnitude of cardiac remodeling across published cohorts. LDH = lactate dehydrogenase; ACS = acute chest syndrome; TRV = tricuspid regurgitant jet velocity; CVA = cerebrovascular accident; LV = left ventricle.

3.8. Correlation of Cardiac Remodeling with Clinical Severity

Table *3* presents the correlations between cardiac remodeling parameters and clinical severity markers across the included studies.

Table 3. Correlation of Cardiac Remodeling with Clinical Severity Parameters.

Cardiac Parameter	Clinical Severity Marker	Studies Reporting	Direction	Statistical Significance
LV Dilation (↑LVEDD)	Annual admissions	[19,31,34]	Positive	p=0.003–0.04
LV Dilation (↑LVEDD)	ACS episodes	[19,27,35]	Positive	p=0.02–0.05
TRV elevation (≥2.5 m/s)	LDH elevation	[17,19,35,45]	Positive	p<0.001–0.01
TRV elevation (≥2.5 m/s)	Prior ACS	[19,35,39]	Positive	p=0.02–0.04
TRV elevation (≥2.5 m/s)	Reticulocyte count	[24,35]	Positive	p=0.01–0.03
Diastolic dysfunction	Hemolytic markers (LDH)	[12,25,40]	Positive	p=0.001–0.03
Diastolic dysfunction	Hb level (inverse)	[40,42]	Negative	p<0.001–0.02
Myocardial fibrosis (ECV)	Transfusion burden	[43,44]	Positive	p=0.004–0.02
Myocardial fibrosis (ECV)	Diastolic dysfunction	[43,44]	Positive	r=0.54, p<0.001
QTc prolongation	LDH elevation	[42]	Positive	r=0.31, p=0.002
QTc prolongation	Hb level (inverse)	[42]	Negative	r=-0.38, p<0.001
LV GLS impairment	Endothelial dysfunction markers	[38]	Positive	p<0.001

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RV dysfunction	TRV elevation	[15,17,45]	Positive	p<0.01
Mortality	TRV ≥2.5 m/s	[17,45]	Positive	HR=3.5, p=0.007
Severity not reported	—	[16,20,22,23,25,26,28–30,32,33,36,37]	N/A	N/A

Legend: LV = left ventricle; LVEDD = left ventricular end-diastolic diameter; TRV = tricuspid regurgitant jet velocity; ACS = acute chest syndrome LDH = lactate dehydrogenase; Hb = haemoglobin; ECV = extracellular volume fraction; GLS = global longitudinal strain; RV = right ventricle; HR = hazard ratio; Note: 13 of 37 studies (35.1%) did not report clinical severity parameters, limiting correlation analysis in these cohorts.

3.9. Correlation of Cardiac Remodeling with SCD Genotype

Table 4. Correlation of Cardiac Remodeling Parameters with SCD Genotype.

Cardiac Parameter	HbSS (%)	HbSC (%)	HbS/β-thal (%)	*p*-value (SS vs. SC)	Studies
LV Dilation	45–55%	20–30%	35–45%	*p*=0.01–0.04	[10,19,21,25,27,31]
TRV≥2.5m/s	25–32%	10–18%	18–25%	*p*=0.02–0.05	[17,19,35,45]
Diastolic dysfunction	28–38%	12–20%	20–28%	*p*=0.01–0.03	[12,25,40,42]
QTc prolongation	26%	12%	18%	*p*=0.04	[42]
Myocardial fibrosis (ECV)	35–40%	NR	20–25%	N/A	[43,44]
LVGLS impairment	Severe	Mild	Moderate	*p*<0.05	[10,38]
Restrictive physiology	13%	Rare	5–8%	*p*<0.05	[41]
Cardiac mortality	Higher	Lower	Intermediate	*p*=0.02	[45]

Legend: HbSS=homozygous sickle cell disease; HbSC=compound heterozygous sickle-hemoglobin C; HbS/β-thal=sickle/β-thalassemia; NR=not reported; ECV=extracellular volume fraction; GLS=global longitudinal strain. p-values represent HbSS vs. HbSC comparisons unless otherwise stated. Geno type not reported in 8/37studies [16,18,20,22,23,26,28–30,32,33,36,37].

3.10. Comparison of Group A (Pediatric-Only) vs. Group B (Mixed-Age) Studies

Table 5. presents the statistical comparison between Group A and Group B studies.

Parameter	Group A: Pediatric-Only (n=31 studies)	Group B: Mixed-Age (n=6 studies)	p-value
Total patients enrolled	~3,785	~468	—
Mean age range	1–18 years	8–40 years	—
Primary modality: 2D Echo	30/31 (96.8%)	5/6 (83.3%)	p=0.22
TDI used	10/31 (32.3%)	4/6 (66.7%)	p=0.09
Cardiac MRI used	**1/31 (3.2%)**	**3/6 (50.0%)**	**p=0.004**
STE used	3/31 (9.7%)	1/6 (16.7%)	p=0.52
LV dilation reported	29/31 (93.5%)	4/6 (66.7%)	p=0.04
Diastolic dysfunction reported	14/31 (45.2%)	5/6 (83.3%)	p=0.09
PH/TRV elevation reported	13/31 (41.9%)	3/6 (50.0%)	p=0.68
Myocardial fibrosis reported	**1/31 (3.2%)**	**3/6 (50.0%)**	**p=0.004**

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Restrictive cardiomyopathy	0/31 (0%)	1/6 (16.7%)	p=0.16
QTc prolongation	0/31 (0%)	1/6 (16.7%)	p=0.16
Genotype data reported	24/31 (77.4%)	6/6 (100%)	p=0.32
Clinical severity data reported	18/31 (58.1%)	6/6 (100%)	p=0.07
Longitudinal design	5/31 (16.1%)	3/6 (50.0%)	p=0.07
Hydroxyurea effect reported	2/31 (6.5%)	1/6 (16.7%)	p=0.41
High NOS/JBI quality score	18/31 (58.1%)	5/6 (83.3%)	p=0.23

In Table 5, the comparison of Group A (Pediatric-Only, [10]-[40]) vs. Group B (Mixed-Age, [41]-[46]). Statistical comparisons used chi-square or Fisher's exact test. Cardiac MRI use (p=0.004) and myocardial fibrosis detection (p=0.004) were significantly more common in mixed-age studies, reflecting greater availability of advanced imaging in adult-inclusive cohorts and the progressive nature of fibrotic remodeling with age. LV = left ventricle; TDI = tissue Doppler imaging; MRI = magnetic resonance imaging; STE = speckle-tracking echocardiography; PH = pulmonary hypertension; TRV = tricuspid regurgitant jet velocity; NOS = Newcastle-Ottawa Scale; JBI = Joanna Briggs Institute.

4. Discussion

4.1. Overview of the Systematic Evidence Base

This systematic review synthesizes data on cardiac remodeling from 37 published studies, encompassing approximately 4,847 patients with SCD across 18 countries and spanning 46 years of research (1978–2024). The broad geographic representation, including Sub-Saharan Africa [14,24,28,30,34], the Middle East [15,26,31,36–38], North America [12,17,19–21,25,27,35,39,45,46], Europe [10,13,16,40], South America [29], South Asia [22,33], and the Caribbean [23,32], underscores the global burden of SCD and highlights the universality of cardiac involvement across diverse genetic and environmental backgrounds. The consistent identification of LV dilation, diastolic dysfunction, and pulmonary hypertension across culturally and geographically diverse cohorts supports the conclusion that cardiac remodeling is an intrinsic, early consequence of SCD pathophysiology rather than a regionally specific phenomenon.

4.2. The Pattern of Cardiac Remodeling: A Developmental Trajectory

4.2.1. The Hyperdynamic State and LV Eccentric Remodeling

The earliest and most common cardiac manifestation of SCD in children is a hyperdynamic circulatory state caused by chronic hemolytic anemia. Seminal studies by Rees et al. [32] and Chung et al. [23] in the late 1970s and 1980s showed that children with HbSS have significantly higher cardiac output, LV dilation, and stroke volume than age-matched controls, despite a preserved ejection fraction. This finding has been consistently replicated over five decades and across multiple continents [14,20,28,29,33]. The pathophysiological mechanism is chronic volume overload secondary to compensatory high-output anemia, which leads to eccentric LV hypertrophy through serial sarcomere replication, thereby increasing LV cavity dimensions while initially maintaining wall thickness and systolic function [1,3].

The trajectory of LV dilation appears to be progressive and age-dependent. Longitudinal data from Harrington et al. [27] demonstrated statistically significant increases in LV end-diastolic dimensions over 4 years of follow-up in children with HbSS ($p < 0.01$), while Giray et al. [40] confirmed progressive deterioration of TDI parameters over 5 years, particularly in HbSS patients. This longitudinal evidence indicates that cardiac remodeling in SCD is not fixed but a progressive cardiomyopathic process that, if left untreated, may culminate in advanced phenotypes, restrictive

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physiology [41], myocardial fibrosis [43,44], and reduced exercise capacity [44] observed in young adult SCD patients.

4.2.2. Diastolic Dysfunction: An Early and Underdiagnosed Manifestation

Identifying diastolic dysfunction as an early and prevalent finding, documented in 48.6% of TDI-based studies, is among the most clinically significant findings of this review. Conventional 2D echocardiography, used in 94.6% of studies, consistently underestimates diastolic dysfunction because of its limited sensitivity to subtle abnormalities in myocardial relaxation. Studies employing TDI [12,25,36,40] and STE [10,15,38] consistently detected higher rates of subclinical dysfunction than those relying solely on conventional echocardiographic parameters. Ghaderian et al. [36] found that reduced TDI-derived E′ velocity and elevated E/E′ ratio were present in 30% of children with HbSS, even when conventional echocardiographic parameters were normal. This finding has significant implications for screening strategies, as reliance on conventional echocardiography alone will systematically miss early diastolic dysfunction in a substantial proportion of children with SCD.

The association between myocardial fibrosis (elevated ECV on cardiac MRI) and diastolic dysfunction, demonstrated by Niss et al. [43] ($r = 0.54$, $p < 0.001$) and Alsaied et al. [44], provides mechanistic insight into this relationship and establishes cardiac MRI as a necessary tool for comprehensive cardiac assessment of older SCD patients [2,9].

4.2.3. Pulmonary Hypertension: A Marker of Hemolytic Severity

Pulmonary hypertension, defined by TRV ≥2.5 m/s, emerged as a consistent and prognostically significant finding, reported in 37.8% of studies, with prevalence ranging from 15% to 32% in pediatric cohorts. The landmark study by Lee et al. [17] established the mortality significance of elevated TRV in children, demonstrating a 3.5-fold increased risk of death ($p = 0.007$), a finding corroborated in the mixed-age cohort by Shah et al. [45] using Cox regression analysis. The association between elevated TRV and hemolytic markers has been repeatedly demonstrated across multiple studies [19,24,35,45], supporting the hemolysis-vasculopathy axis as the primary driver of pulmonary vascular disease in SCD [4,8].

The finding by Colombatti et al. [13] that elevated TRV is detectable in children as young as 1–2 years with HbSS is particularly alarming, suggesting that pulmonary vascular disease may begin in infancy and progress silently throughout childhood. This necessitates early and systematic echocardiographic screening beginning in the first years of life [6].

4.2.4. Myocardial Fibrosis: The Advanced Remodeling Phenotype

Myocardial fibrosis, detectable by cardiac MRI ECV mapping, represents the most advanced form of cardiac remodeling in SCD and has been reported exclusively in mixed-age studies [11,43,44]. Only Wagdy et al. [11] identified subclinical fibrosis in a purely pediatric cohort, using galectin-3 as a surrogate biomarker. The clinical significance is considerable: Niss et al. [43] demonstrated an association with diastolic dysfunction, while Alsaied et al. [44] linked it to reduced exercise capacity and left atrial dysfunction, both of which are indicative of progressive heart failure. Collectively, these findings suggest that the fibrotic remodeling phenotype, although fully manifest in young adults, likely originates from repeated ischemic and inflammatory insults during childhood SCD [9].

4.3. Genotype and Cardiac Remodeling: A Consistent Hierarchy

4.3.1. HbSS: The Most Severe Cardiac Phenotype

The HbSS genotype was consistently associated with the most severe cardiac remodeling across all assessed parameters in studies with genotype-stratified data [10,17,19,21,25,27,31,35,40,42,45]. Minniti et al. [19] demonstrated significantly higher TRV in HbSS versus HbSC children ($p < 0.05$), while Liem et al. [42] reported QTc prolongation.

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in 26% of HbSS versus 12% of HbSC patients (p = 0.04). Harrington et al. [27] reported more rapid longitudinal progression of LV dilation in HbSS than in HbSC (p < 0.01). This hierarchy reflects higher hemolysis rates, lower steady-state hemoglobin levels, and a higher frequency of vaso-occlusive complications in HbSS compared with compound heterozygous genotypes [3,5].

4.3.2. HbS/β-Thalassemia: An Intermediate Phenotype

HbS/β-thalassemia, particularly the HbS/β0 subtype, has been reported to exhibit an intermediate cardiac phenotype, more severe than HbSC but generally milder than HbSS, in studies of this genotype [10,13,16,31,40]. The distinction between β0 (no β-chain production) and β+ (reduced β-chain production) subtypes is clinically important, as HbS/β0-thalassemia approaches HbSS in clinical severity. Studies that did not differentiate between these subtypes [21,25] may have underestimated cardiac severity in patients with HbS/β0-thalassemia.

4.3.3. HbSC: A Milder but Not Benign Phenotype

Although HbSC disease is associated with milder hemolysis and higher steady-state hemoglobin levels, it is not free of cardiac complications. In HbSC, these complications are driven by arterial hypertension and comorbid overweight [47]. Batra et al. [21] documented LV dilation in 20–30% of HbSC children, and Shah et al. [45] demonstrated that elevated TRV also predicted mortality in HbSC patients, though at lower absolute rates than in HbSS. This finding challenges the historical perception of HbSC as a benign condition and supports systematic cardiac screening across all SCD genotypes, not solely HbSS.

4.4. Clinical Severity Correlates of Cardiac Remodeling

4.4.1. Hemolytic Markers

The correlation between hemolytic intensity, as reflected by LDH elevation, indirect bilirubin, and reticulocyte count, and the severity of cardiac remodeling was the most consistently observed association in this review [17,19,24,35,42,45]. LDH elevation correlated with TRV elevation (p < 0.001–0.01), diastolic dysfunction (p = 0.001–0.03), and QTc prolongation (r = 0.31, p = 0.002). This association is mechanistically grounded in the hemolysis-NO depletion-vasculopathy pathway [4,8], which drives both pulmonary vascular disease and myocardial injury.

4.4.2. Acute Chest Syndrome and Vaso-Occlusive Crises

Previous ACS episodes were correlated with elevated TRV in multiple studies [19,35,39], likely reflecting pulmonary vascular injury and hypoxic insults associated with recurrent ACS. Onalo et al. [34] demonstrated transient worsening of LV diastolic function during acute vaso-occlusive crises, with partial recovery afterward, suggesting that each episode contributes incrementally to cumulative cardiac remodeling.

4.4.3. Transfusion Burden and Hydroxyurea

Hankins et al. [12] found no evidence of myocardial iron deposition on cardiac MRI T2* in a predominantly pediatric cohort, suggesting that iron-mediated cardiac injury may be less prevalent in children than in adults, possibly due to shorter cumulative transfusion exposure. However, the association between transfusion burden and myocardial fibrosis observed in adult studies [43,44] underscores the need for vigilant iron monitoring in heavily transfused children.

Hydroxyurea therapy, as evaluated by Dhar et al. [46], significantly attenuated progression of LV dilation in pediatric SCD patients (p < 0.05), consistent with its mechanism of action, which includes increasing fetal hemoglobin (HbF), reducing sickling and hemolysis, and decreasing the frequency of vaso-occlusive events. This finding has direct clinical implications and supports early initiation of hydroxyurea as a cardioprotective strategy [6,7].

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4.5. Comparison of Pediatric-Only vs. Mixed-Age Studies

The comparison of Group A and Group B studies showed that mixed-age studies were significantly more likely to use cardiac MRI (50% vs. 3.2%, p = 0.004) and to report myocardial fibrosis (50% vs. 3.2%, p = 0.004), indicating an advanced remodeling phenotype in older patients and greater MRI feasibility in adult cohorts. Conversely,

Pediatric-only studies more often reported LV dilation (93.5% vs. 66.7%, p = 0.04), underscoring the central role of the hyperdynamic state and eccentric remodeling in the pediatric cardiac phenotype.

The mixed-age studies [41–46] provide a critical longitudinal perspective on the natural history of cardiac remodeling in SCD. The restrictive cardiomyopathy [41], diffuse myocardial fibrosis [43,44], and mortality-predictive TRV elevation [45] observed in young adults represent the endpoint of a remodeling process that begins in childhood. The progression from hyperdynamic LV dilation in infancy [28,32] to diastolic dysfunction in school-age children [12,36] and ultimately to myocardial fibrosis in adolescence and young adulthood [43,44] constitutes a coherent, progressive cardiomyopathic continuum. Systolic dysfunction is rare in SCD patients with cardiomyopathy [48].

4.6. Methodological Considerations and Quality Assessment

Methodological heterogeneity across the 37 studies poses a significant challenge for quantitative synthesis. Echocardiographic protocols ranged from basic M-mode measurements [20,23,32] to advanced 3D STE [37,38], complicating direct comparisons of cardiac parameters. The lack of standardized z-score reporting in many studies [18,26,30] limits comparability of LV dimensional data across age groups. The predominance of cross-sectional designs (27/37 studies; 73%) restricts causal inference and precludes assessment of temporal remodeling trajectories.

4.7. Evidence-Based Screening Recommendations

Based on the synthesized evidence, the following recommendations are presented for pediatric and adolescent SCD patients:

Baseline echocardiography at diagnosis (or by age 2 years) for all SCD patients, with annual follow-up in HbSS and HbS/β0-thalassemia.

TDI and/or STE should be incorporated into routine echocardiographic protocols used to detect subclinical diastolic and systolic dysfunction that may not be apparent on conventional imaging.

TRV measurement at every echocardiographic assessment; TRV ≥2.5 m/s should trigger further evaluation, including BNP measurement and consideration of right heart catheterization.

Cardiac MRI (ECV mapping) in adolescents and young adults with progressive cardiac symptoms, unexplained diastolic dysfunction, or heavy transfusion burden.

ECG with QTc measurement annually in adolescents and young adults.

Galectin-3 and BNP/NT-proBNP as emerging non-invasive biomarkers for fibrosis and cardiac stress monitoring.

5. Conclusions and Recommendations

This systematic review establishes the following data-driven conclusions:

1. **Cardiac remodeling is universal and early in pediatric SCD**, beginning in the first years of life and progressing throughout childhood and adolescence. LV eccentric dilation and hyperdynamic circulation are the earliest and most prevalent manifestations.
2. **HbSS genotype carries the most severe cardiac phenotype** across all remodeling parameters, followed by HbS/β-thal and HbSC.
3. **Clinical severity correlates significantly with cardiac remodeling.** Hemolytic intensity, ACS frequency, and annual hospitalization rates are the strongest clinical predictors of cardiac remodeling severity.

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4. Advanced imaging modalities (TDI, STE, cardiac MRI) reveal subclinical dysfunction missed by conventional echocardiography in 20–40% of children.
5. Myocardial fibrosis represents the end-stage of pediatric cardiac remodeling, presaged in children by elevated galectin-3.
6. **Hydroxyurea therapy attenuates cardiac remodeling progression** and should be considered a cardioprotective intervention.
7. Significant research gaps remain, including inadequate reporting of clinical severity parameters (35.1% of studies) and genotype data (21.6% of studies).

Recommendations for Future Research:

1. Prospective multicentre longitudinal cohort studies with standardized echocardiographic protocols (including TDI and STE) and systematic severity reporting.
2. Cardiac MRI studies in pediatric SCD populations to characterize the onset of myocardial fibrosis.
3. Randomized controlled trials evaluating cardioprotective interventions (hydroxyurea, iron chelation) with cardiac endpoints.
4. Development and validation of a composite cardiac risk score for pediatric SCD patients

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