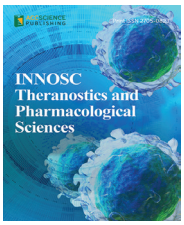
INNOSC Theranostics and Pharmacological Sciences 2023 Vol. 6 (No. 1) pp: 35-45

ACCSCIENCE PUBLISHING

INNOSC Theranostics and Pharmacological Sciences

Journal homepage: https://accscience.com/journal/ITPS



REVIEW ARTICLE

Pulmonary Hypertension among Children and Adolescents with Sickle Cell Anemia: A Systematic Review and Meta-analysis

Vishnu Shankar Hariharan*

Department of Internal Medicine, Hindu Mission Hospital, Chennai, India

***Corresponding author:** Vishnu Shankar Hariharan, *Email:* vishank91@gmail.com

Received: September 16, 2022; ***Accepted:*** April 7, 2023; ***Published:*** April 20, 2023 ***DOI:*** 10.36922/itps.198

Abstract:

Pulmonary hypertension (PHT) is a major life-threatening complication associated with sickle cell anemia (SCA). However, there is scarcity of evidence in pooling the knowledge regarding the prevalence of PHT in the pediatric SCA patients. Hence, this systematic review was done to determine the pooled prevalence of PHT among SCA children and adolescents. Until January 2021, systematic searches were conducted in MEDLINE, SCOPUS, Web of Science, ScienceDirect, Cochrane library, and Google Scholar. The listed studies' caliber was evaluated using the Newcastle Ottawa scale. The results of a meta-analysis using a random-effects model included a pooled prevalence and 95% confidence intervals (CIs). In total, 31 studies with 3686 participants were included in the study. Majority of the included studies (26 out of 31 studies) had low risk of bias. The final pooled prevalence of PHT among children and adolescents with SCA was 22% (95% CI: 18 – 26%). Maximum burden of PHT among SCA children was reported in Europe (26%) and Eastern Mediterranean region, while the least burden was found in Africa (17%). There was a significant heterogeneity found between the studies in our analysis (I^2 = 87.8%; P < 0.001). The presence of publication bias indicated by an asymmetrical funnel plot was also found. About one in five children and adolescents with SCA suffer from PHTN. The burden is maximum in Europe followed by Eastern Mediterranean region. Diagnostic and intervention packages targeting these patients should be developed and implemented across the high-risk settings.

Keywords: Epidemiology, Meta-analysis, Pulmonary hypertension, Sickle cell anemia

1. Introduction

Sickle cell anemia (SCA) is one of the most common inherited genetic hematological condition affecting children and adolescents [1]. It can be characterized by the red cell sickling accompanied by end organ damage due to vaso-occlusion and hemolytic anemia [1]. Almost 5% of the world population were found to be healthy carriers of SCA or thalassemia gene [2]. About 300,000 children are born with severe form of these conditions, with majority occurring in low- and low middle-income countries [2]. SCA is associated with several different complications with varying severity.

Pulmonary hypertension (PHT) is a major life-threatening complication associated with SCA [3]. It is a hemodynamic illness characterized by increased vascular resistance of pulmonary circulation. The previous studies have shown that SCA is frequently associated with PHT among children and adolescents [3,4]. The occurrence of PHT in SCA patients is caused by hemolytic reaction and distorted nitric acid metabolism [5,6]. It may remain clinically silent for prolonged period and can be discovered late during illness. It has

also been reported to be a severe complication of SCA leading to an accelerated death [7]. Hence, PHT occurring secondary to SCA is classified as a separate condition as the mortality due to SCA-PHT can be 10 times higher than SCA patients without PHT [8,9].

A diagnosis of PHT can be established by the right ventricular catheterization with end systolic pressure value ≥25 mmHg. However, there are certain non-invasive methods available to diagnose PHT such as Doppler echocardiography. It can be used to assess the tricuspid valve regurgitant velocity (TRV). TRV ≥2.5 m/s among SCA patients has been established as a surrogate marker for PHT [10-12]. Several studies have made efforts to determine the burden of PHT using TRV among children and adolescents with SCA [13-16]. However, studies have reported wide variation in the prevalence of PHT among SCA children and adolescents. However, there is scarcity in pooling the knowledge regarding the prevalence of PHT in the pediatric SCA patients. Hence, this study was conducted to pool the evidence reporting the PHT among SCA children and adolescents and report a pooled estimate.

2. Materials and methods

2.1. Design

We conducted a systematic review and meta-analysis of observational studies. We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist for reporting systematic reviews incorporating meta-analyses for reporting our review [17].

2.2. Eligibility criteria

2.2.1. Type of studies

For the present study, articles describing the prevalence of PHT among SCA patients were considered. There were no limitations based on the site or design of the study. Unpublished data and grey literature were discarded, but studies with complete texts or abstracts were included.

2.2.2. Type of participants

Studies conducted among children and adolescents (aged up to 19 years), irrespective of their ethnicity, comorbid status, or severity of the condition were included in the study.

2.2.3. Type of outcome measure

Studies reporting the prevalence of PHT and diagnosed it using either the right heart catheterization or transthoracic Doppler echocardiography were included in the study.

2.3. Search strategy

To find relevant information, we created a thorough search strategy and conducted thorough, methodical searches in databases and search engines such as MEDLINE, SCOPUS, Web of Science, ScienceDirect, Cochrane library, and Google Scholar. To conduct the search, we employed free-text headings and MeSH—selected medical subject headings. The phrases "SCA," "PHT," "Pulmonary Arterial Hypertension," "Children," "Adolescent," "Epidemiology," "Prevalence," and "Burden" were used in different combinations in PubMed and other search engines. Without regard to language, the search period was set from the database's establishment through January 2021. In addition, we manually searched for any articles meeting the inclusion criteria and cross-checked the bibliographies of the research we have retrieved.

2.4. Study selection

Title, keyword, and abstract screening — or primary screening — was carried out initially. The complete text of the articles that might meet the eligibility requirements was obtained. The retrieved full texts were then subjected to a further screening to determine their eligibility based on pre-established standards.

2.5. Data extraction

A pre-defined template was used as a data extraction form to obtain the following set of data: authors, title of study, year of publication, study period, study design, setting, country/region, total sample size, sampling criteria, diagnostic tool and measures, cutoff, statistical tests, outcome assessment details, average age, non-response rate, and burden of PHT.

2.6. Risk of bias (quality) assessment

The risk of bias evaluation was done using the Newcastle-Ottawa scale, which has been modified for cross-sectional studies [18]. Six domains and two criteria are used to evaluate the bias risk. The sample representativeness, sample size justification, rate of non-responses, information on non-responders, and use of validated measuring tools are the primary factors associated to participant selection. The second criterion relates to the participants' outcomes and comprises two subdomains: outcome assessment using a blinded, independent assessment and record linkage, and statistical tests used. Based on the degree of bias risk, each of these domains was rated as either high-risk (one point) or low-risk (zero point). Studies having three or more points were considered high risk.

2.7. Statistical analysis

With the final group of chosen studies, a meta-analysis was carried out using STATA 14.2's "metaprop" command package (StataCorp, College Station, TX, USA) [19]. To reduce the impact of extremely tiny or large values on the overall estimate and stabilize the variance, we employed the Freeman Tukey double arcsine transformation [19]. Because of the anticipated heterogeneity, a random effects model was used, and the final data were given as pooled prevalence with a 95% confidence interval (CI). Using a forest plot, these combined estimations were visually shown.

Using the I^2 statistic and the Chi-square of heterogeneity, heterogeneity was assessed. I^2 value was utilized to assess the heterogeneity, and $P < 0.05$ in the Chi-square test indicates significant heterogeneity [20]. Due to the significant heterogeneity in our research, we also conducted subgroup analysis and meta-regression. This strategy was used to investigate the cause of the high level of heterogeneity. A funnel plot was used to examine and depict publication bias. Using Egger's test, we also evaluated the asymmetry of the plot. Publication bias was deemed statistically significant when the *P*-value was 0.10 or higher [21].

3. Results

3.1. Study selection

In primary screening, 189 full-text studies were retrieved, which after removal of duplicates become 171 studies. These studies, in addition to the three articles retrieved from the bibliography of the screened articles, underwent secondary screening. Finally, we included data from 31 studies with 3686 participants satisfying the inclusion criteria (**Figure 1**) [13-16,22-48].

3.2. Study characteristics

Majority of the studies (11 out of 31) were prospective in nature, while 10 studies were retrospective and cross-sectional in nature. Most studies (19 out of 31) were conducted in United States of America (USA) followed by Nigeria (5) and India (2). The mean age of study participants ranged from 6.2 to 16.1 years. The sample sizes among the included studies varied from 20 to 630. All the studies have used transthoracic Doppler ultrasonography to measure tricuspid regurgitation velocity (TRV) for diagnosing PHT. Almost all the studies have used the cutoff 2.5 m/s to diagnose PHT except Nouraie *et al.* that used the cutoff of 2.7 m/s [38]. Regarding the quality assessment, five out of 31 studies were of poorer quality, while all other studies had good quality (**Table 1**).

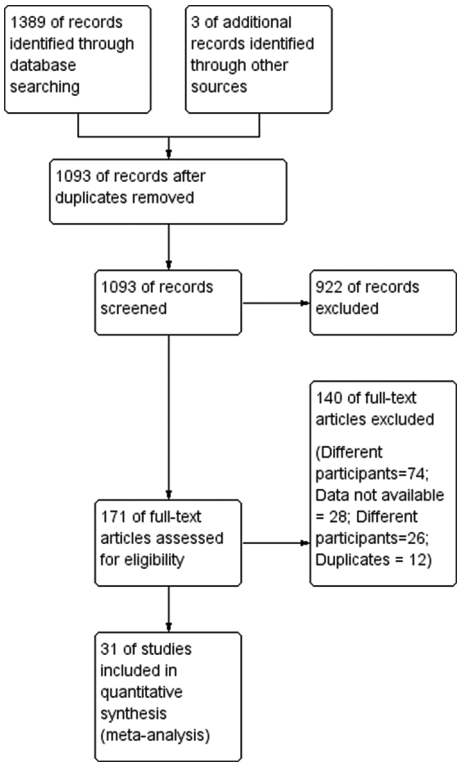


Figure 1. Flowchart showing the search strategy and selection of studies.

Table 1. Characteristics of the included studies (n = 31)

Study no.	First author and year	Region	Country	Study design	Sample size	Study participants	Criteria and cut - off	Mean age (in years)	Quality of evidence
1	Agha *et al*. 2014 [22]	Europe	Egypt	Cross - sectional	80	Children and younger population with SCA under basal conditions	TRJV and 2.5	12.7	High
2	Allen *et al*. 2019 [13]	America	USA	Retrospective	105	Children ≥10 years of age with SCA who underwent an outpatient transthoracic echocardiogram as part of a screening program.	TRJV and 2.5	15	High
3	Ambrusko *et al*. 2006 [14]	America	USA	Retrospective	44	Pediatric SCA patients	TRJV and 2.5	14.8	High
4	Chinawa *et al*. 2020 [15]	Africa	Nigeria	Cross - sectional	51	Children aged 3 years to 17 years, who attended the sickle cell clinics of the study hospitals and were in steady state	TRJV and 2.5	9.7	High
5	Colombatti *et al*. 2010 [16]	Europe	Italy	Prospective	37	SCA children >3 years old at steady state	TRJV and 2.5	6.2	High
6	Cox *et al*. 2014 [23]	Africa	Tanzania	Prospective	215	Children and adolescents aged 9–19 years, HbSS by hemoglobin electrophoresis and high - performance liquid chromatography for SCA	TRJV and 2.5	14.1	High
7	Dahoui *et al*. 2010 [24]	EMR	Lebanon	Prospective	85	All patients with hemoglobin SS, Sb0thal, or Sbþthal seen at the comprehensive sickle cell clinic at Children's Cancer Center of Lebanon	TRJV and 2.5	12.9	High
8	Eddine *et al*. 2012 [25]	America	USA	Retrospective	40	Children with SCA	TRJV and 2.5	14.2	High
9	Forrest *et al*. 2012 [26]	America	USA	Retrospective	85	Children with Hb SS and Hb Sb0 thalassemia older than 6 years of age	TRJV and 2.5	12.1	High

(*Cont'd...*)

Table 1. (*Continued*)

Study no.	First author and year	Region	Country	Study design	Sample size	Study participants	Criteria and cut - off	Mean age (in years)	Quality of evidence
10	Gordeuk *et al*. 2011 [27]	America	USA	Prospective	160	Participants with SCA who had clinical evaluation, echocardiography and 6 - min walk test performed at steady - state	TRJV and 2.5	13	High
11	Gore *et al*. 2018 [28]	SEAR	India	Cross - sectional	38	Children with SCA	TRJV and 2.5	NA	High
12	Hagar *et al*. 2007 [29]	America	USA	Retrospective	61	Children with SCA	TRJV and 2.5	12.7	High
13	Hebson *et al*. 2015 [30]	America	USA	Retrospective	630	Children with SCA	TRJV and 2.5	11.7	High
14	Jesus Rojas *et al*. 2018 [31]	America	USA	Prospective	29	Children with SCA	TRJV and 2.5	NA	High
15	Lamina *et al*. 2019 [32]	Africa	Nigeria	Cross - sectional	200	SCA children aged 1 to 12 years attending the sickle cell clinic who were in steady state	TRJV and 2.5	6.6	Low
16	Liem *et al*. 2007 [33]	America	USA	Prospective	51	Children with SCA	TRJV and 2.5	14	High
17	Liem *et al*. 2009 [34]	America	USA	Prospective	78	Children with SCA	TRJV and 2.5	14.3	High
18	Minniti *et al*. 2009 [35]	America	USA	Prospective	310	Children and adolescents with SCA	TRJV and 2.5	13	High
19	Molavi *et al*. 2014 [36]	EMR	Iran	Retrospective	70	Children with SCA	TRJV and 2.5	NA	High
20	Mondal *et al*. 2018 [37]	America	USA	Retrospective	20	Children with SCA	TRJV and 2.5	10.4	High
21	Nelson *et al*. 2007 [38]	America	USA	Prospective	53	SCA patients under the age of 10 years	TRJV and 2.5	12.4	High
22	Nouraie *et al*. 2020 [39]	America	USA	Prospective	469	Children and adolescents with SCA	TRJV and 2.7	12	High
23	Onalo *et al*. 2020 [40]	Africa	Nigeria	Cross - sectional	176	Children with SCA	TRJV and 2.5	10.4	Low
24	Onyekwere *et al*. 2008 [41]	America	USA	Cross - sectional	52	Children and adolescents with SCA	TRJV and 2.5	16.1	High
25	Pashankar *et al*. 2008 [42]	America	USA	Prospective	62	Children with SCA	TRJV and 2.5	13.5	High

(*Cont'd...*)

Table 1. (*Continued*)

Study no.	First author and year	Region	Country	Study design	Sample size	Study participants	Criteria and cut - off	Mean age (in years)	Quality of evidence
26	Patel *et al*. 2016 [43]	SEAR	India	Cross - sectional	50	All patients between the age group of 5 to 18 years diagnosed to have sickle cell syndromes	TRJV and 2.5	11.3	Low
27	Peter *et al*. 2019 [44]	Africa	Nigeria	Cross - sectional	100	SCA subjects 3–14 years of age in their steady state	TRJV and 2.5	7	Low
28	Qureshi *et al*. 2006 [45]	America	USA	Retrospective	32	Children with SCA	TRJV and 2.5	8.9	High
29	Sedak *et al*. 2009 [46]	America	USA	Cross - sectional	48	Children with SCA	TRJV and 2.5	12	High
30	Sokunbi *et al*. 2017 [47]	Africa	Nigeria	Cross - sectional	175	SCA subjects with haemoglobin genotype SS aged 5 – 18 years	TRJV and 2.5	8.8	Low
31	Suell *et al.* 2005 [48]	America	USA	Retrospective	80	Children with SCA	TRJV and 2.5	15.6	High

EMR: Eastern Mediterranean region; NA: not available; SCA: sickle cell anemia; SEAR: South East Asian region; TRJV: tricuspid valve jet velocity; USA: United States of America

3.3. Burden of PHT in SCA children and adolescents

The final pooled prevalence of PHT among children and adolescents with SCA was 22% (95%CI: 18 – 26%) **(Figure 2)**. Country-wise distribution of PHT is depicted in **Figure 3**. Maximum burden of PHT among SCA children was reported in Europe (26%) and Eastern Mediterranean region (EMR), while the least burden was found in Africa (17%). There was a significant heterogeneity found between the studies in our analysis (I^2 = 87.8%; P < 0.001). Meta-regression was done to find the source of heterogeneity.

3.4. Meta-regression

We included that the following potential covariates for meta-regression were study design, region, quality of evidence, mean age, and year of publication. All these factors had p-value < 0.20 in the univariable model, and they were included to perform multivariable meta-regression analysis. The adjusted model was able to explain 100% of the between-study variability and the model was statistically significant (P = 0.01). Quality of evidence, mean age, and study design were found to be the significant source of heterogeneity in the adjusted model with $P < 0.05$.

3.5. Publication bias

Egger's test was performed for the assessment of publication bias. There were significant small study effects with coefficient value (coefficient: 1.31; P = 0.002) which shows possibility of publication bias. Graphical representation of the test of publication bias is depicted using funnel plot in **Figure 4**. The funnel plot also shows asymmetric plot indicating the presence of publication bias.

4. Discussion

This review was conducted to obtain a comprehensive estimate for burden of PHT among children and adolescents with SCA. In total, we analyzed data from 31 studies with 3,686 participants. Most of the studies were conducted in USA followed by Nigeria and India. Majority of the included studies had lower risk of bias. Significant

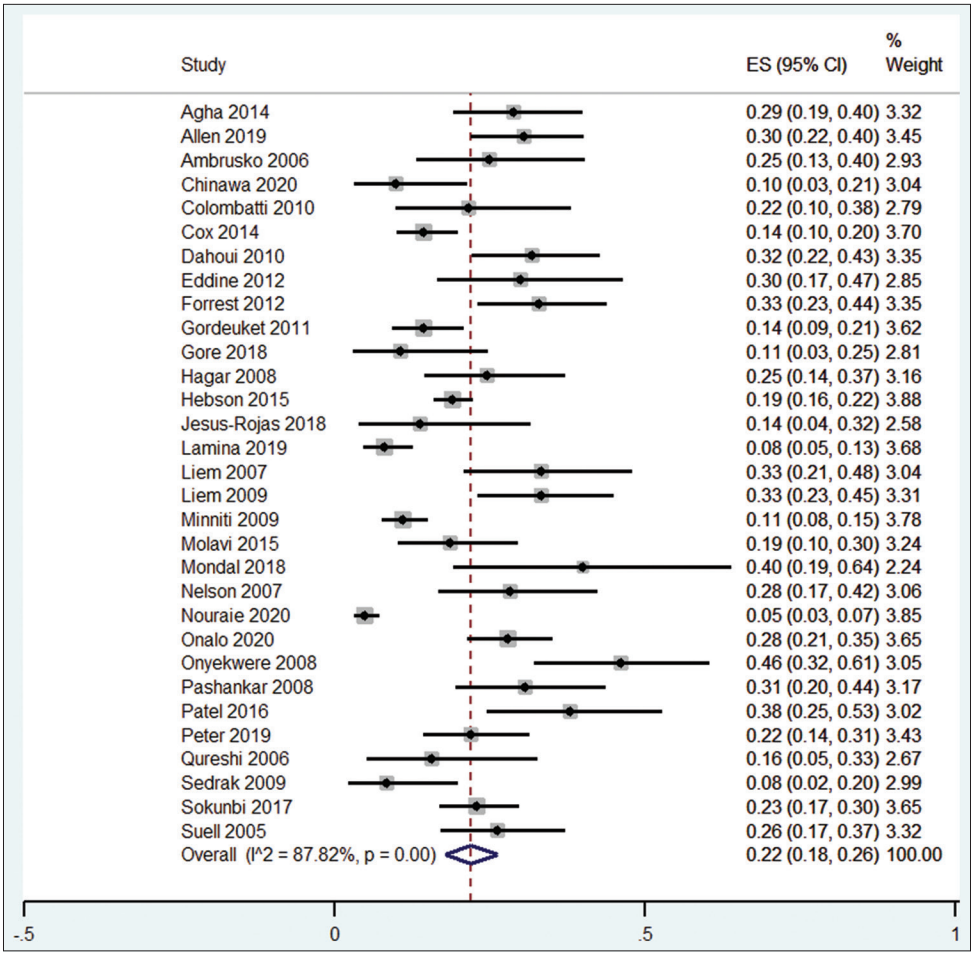


Figure 2. Forest plot showing the prevalence of pulmonary hypertension among sickle cell anemia children and adolescents (n = 31).

heterogeneity was found among the included studies. Hence, meta-regression was performed and found that quality of evidence, mean age, and study design are potential source of heterogeneity in this review. The presence of publication bias indicated by asymmetrical funnel plot was also found.

The prevalence of PHT among children and adolescents with SCA was 22% (95% CI: 18 – 26%). The previous reviews on PHT focused primarily on the participants with SCA irrespective of their age group or general population or special groups such as acquired immunodeficiency syndrome (AIDS) patients, end-stage renal disease patients, and systemic sclerosis patients [49-53]. Our findings were almost similar to the previous review reporting the prevalence of PHT among adult SCA patients [49]. This indicates that there is not much variation in the burden of PHT among SCA patients, irrespective of their age group. Hence, equal importance should be given to all the SCA patients as the risk of PHT is similar across the groups. In addition, we found the burden of PHT in SCA patients to be higher than those in general population or special groups suh as AIDS patients and systemic sclerosis patients [50,51,53]. However, it was significantly lower compared to patients with cardiac, respiratory, or renal comorbid conditions [51,52]. However, most of the studies included in the current review and previous reviews have used TRV to determine the burden of PHT. This tends to overestimate the prevalence as the definition of PHT with echocardiography is still a matter of continuous debate. This is because TRV of 2.5 m/s reflects a right ventricular systolic pressure of 27 mmHg plus right atrial pressure, a pressure far from being relevant for pulmonary vasculopathy. Hence, it is mandatory to use cardiac catheterization when defining PHT, and the future studies should focus on doing it to establish the burden of PHT. Still, the findings from this

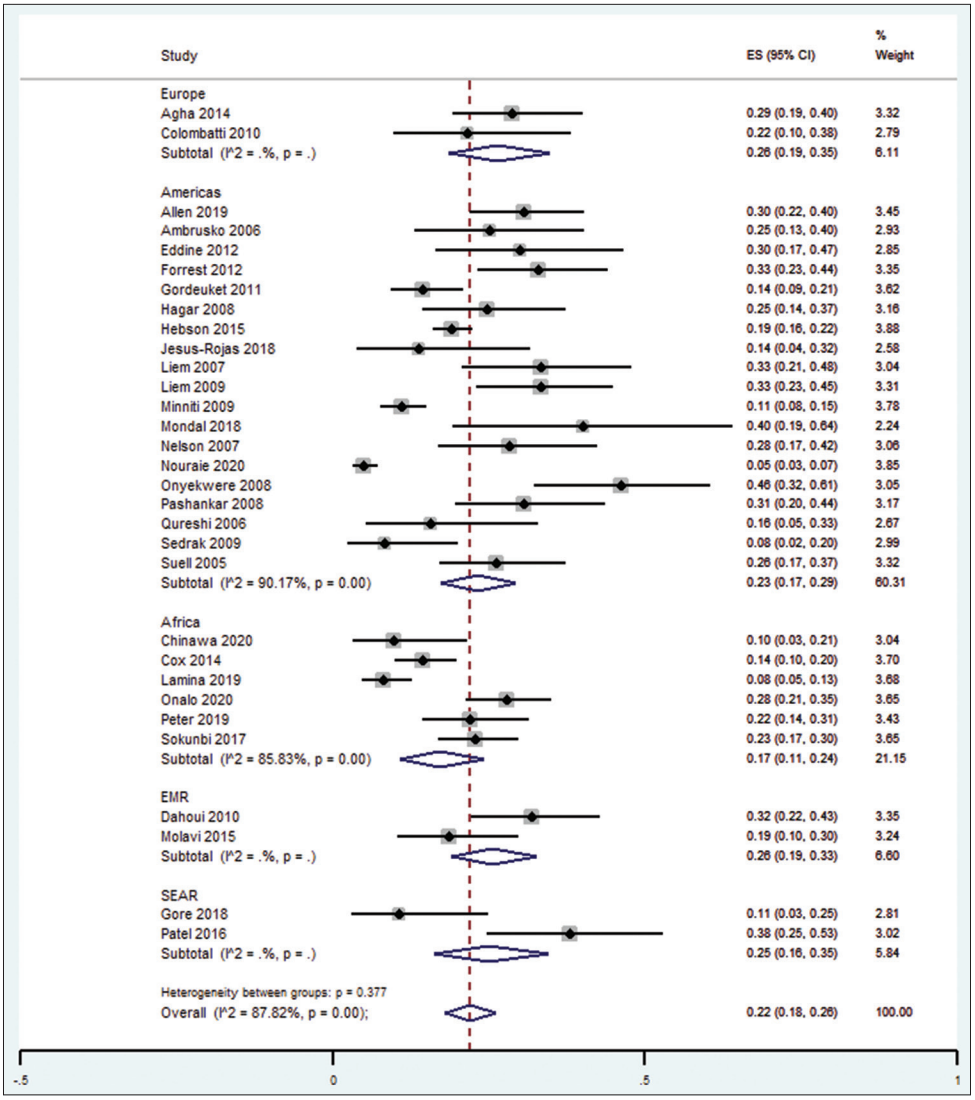


Figure 3. Forest plot showing the region-wise subgroup analysis of pulmonary hypertension burden among sickle cell anemia children and adolescents (n = 31).

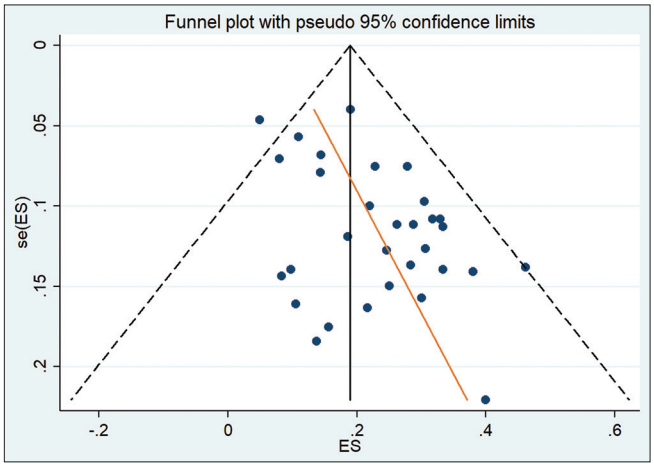


Figure 4. Funnel plot for checking the possibility of publication bias (n = 31).

systematic review highlight the need for screening all the children and adolescents with SCA using TRV as a screening procedure, and the children diagnosed to have PHT using TRV can undergo cardiac catheterization for further confirmation.

Subgroup analysis was performed to see whether there is any variation in the burden across the regions. We found that the SCA children and adolescents in Europe and EMR had the highest burden of PHT, while Africa had the least prevalence. The previous review has also found that the burden of PHT was higher in the European region and lesser in the African region [49]. Although the number of patients with SCA is higher among the people in African region, the burden of PHTN is lesser when compared to European region. This difference in the burden can be attributed to the better diagnostic tool availability in high-income region like Europe. It may also be due to lack of access to diagnostic

care in the African countries. Availability, accessibility, and affordability of the diagnostic and therapeutic care in Europe may improve the survival of the patients, thereby showing a comparatively higher prevalence in the region. Hence, there is a need to close the gap in providing care for the SCA patients between Europe and Africa. This calls for the development of simple, non-invasive, and cost-effective tools for screening the patients, as it ultimately leads to early diagnosis and adequate management of the condition. Using right heart catheterization as a screening tool is not practically possible due to lack of trained/skilled human resources in such low-income/high-SCA-burden countries in Africa. TRV screening can be considered a more pragmatic option for screening the SCA patients for PHT in such settings. There is also availability of many biomarkers that suggest the presence of PHT and can be used as an effective screening tool [54].

The major strength of the study is that this is so far the first comprehensive review on burden of PHT among the younger population with SCA globally. We have also included large number of studies to provide reasonable estimate on the burden. However, our review had certain limitations. All the included studies have used TRV to diagnose PHT. This can overestimate the prevalence as the right heart catheterization is the gold standard for diagnosing a case of PHT. The Chi-square test for heterogeneity also revealed significant variability across the included studies. This limitation was overcome in this work by conducting meta-regression to explain the between-study variability using meta-regression and identify the potential sources of heterogeneity. Significant publication bias was also found, indicating that the point estimate obtained in our review should be interpreted with caution.

5. Conclusions

Current review provides important baseline information on the epidemiology of PHT among children and adolescents with SCA in the world. The findings of this systematic review highlight that PHT is one of the important complications among SCA patients irrespective of their age. This review also highlights the fact that only fewer studies have investigated the extent of PHT among the SCA patients in lower- and lower middle-income regions. Diagnostic and intervention packages targeting these patients should be developed and implemented by clinicians across the high-risk settings. Further studies on exploring the factors responsible for high burden of PHT among SCA patients should be done as it will help the clinicians to understand the mechanism and take decisive actions and implement patient-specific interventions accordingly.

Acknowledgments

None.

Funding

None.

Conflict of interest

The author declares no conflicts of interests.

Author contributions

This is single-authored manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

References

[1] World Health Organization. Sickle-Cell Disease and Other Haemoglobin Disorders WHO, Geneva. Available from: https://apps.who.int/iris/bitstream/handle/10665/20890/A59_9-en.pdf?sequence=1&Isallowed=y [Last accessed on 2022 Feb 11].

[2] World Health Organization. Sickle-Cell Disease. WHO, Geneva. Available from: https://www.afro.who.int/health-topics/sickle-cell-disease [Last accessed on 2021 Feb 11].

[3] Gladwin, M.T. Current and Future Therapies of Sickle Cell Anaemia: An Historical Perspective. Hematology Am. Soc. Hematol. Educ. Program, **2018**, 176, 417–9.

[4] Haque, A.K.; Gokhale, S.; Rampy, B.A.; Adegboyega, P.; Duarte, A.; Saldana, M.J. Pulmonary Hypertension in Sickle Cell Hemoglobinopathy: A Clinicopathologic Study of 20 Cases. Hum. Pathol., **2002**, 33, 1037–43.

[5] Rother, R.P.; Bell, L.; Hillmen, P.; Gladwin, M.T. The Clinical Sequelae of Intravascular Hemolysis and Extracellular Plasma Hemoglobin: A Novel Mechanism of Human Disease. JAMA, **2005**, 293, 1653–62.

[6] Reiter, C.D.; Wang, X.; Tanus-Santos, J.E.; Hogg, N.; Cannon, R.O 3rd.; Schechter, A.N.; Gladwin, M.T. Cell-Free Hemoglobin Limits Nitric Oxide Bioavailability in Sickle-Cell Disease. Nat. Med., **2002**, 8, 1383–9.

[7] Mehari, A.; Gladwin, M.T.; Tian, X.; Machado, R.F.; Kato, G.J. Mortality in Adults With Sickle Cell Disease and Pulmonary Hypertension. JAMA, **2012**, 307, 1254–6.

[8] Parent, F.; Bachir, D.; Inamo, J.; Lionnet, F.; Driss, F.; Loko, G.; Habibi, A.; Bennani, S.; Savale, L.; Adnot, S.; Maitre, B.; Yaïci, A.; Hajji, L.; O'Callaghan, D.S.; Clerson, P.; Girot, R.; Galacteros, F.; Simonneau, G. A Hemodynamic Study of Pulmonary Hypertension in Sickle Cell Disease. N. Engl. J. Med., **2011**, 365, 44–53.

[9] De Castro, L.M.; Jonassaint, J.C.; Graham, F.L.; Ashley-Koch, A.; Telen, M.J. Pulmonary Hypertension Associated with Sickle Cell Disease: Clinical and Laboratory Endpoints and Disease Outcomes. Am. J. Haematol., **2008**, 83, 19–25.

[10] Gladwin, M.T.; Sachdev, V.; Jison, M.L.; Shizukuda, Y.; Plehn, J.F.; Minter, K.; Brown, B.; Coles, W.A.; Nichols, J.S.; Ernst, I.; Hunter, L.A.; Blackwelder, W.C.; Schechter, A.N.; Rodgers, G.P.; Castro, O.; Ognibene, F.P. Pulmonary Hypertension as a Risk Factor for Death in Patients with Sickle Cell Disease. N. Engl. J. Med., **2004**, 350, 886–95.

[11] Ataga, K.I.; Moore, C.G.; Jones, S.; Olajide, O.; Strayhorn, D.; Hinderliter, A.; Orringer, E.P. Pulmonary Hypertension in Patients with Sickle Cell Disease: A Longitudinal Study. Br. J. Haematol., **2006**, 134, 109–15.

[12] Castro, O.; Gladwin, M.T. Pulmonary Hypertension in Sickle Cell Disease: Mechanisms, Diagnosis, and Management. Hematol. Oncol. Clin. North. Am., **2005**, 19, 881–96.

[13] Allen, K.Y.; Jones, S.; Jackson, T.; DeCost, G.; Stephens, P.; Hanna, B.D.; Cohen, M.S; Smith-Whitley, K.; Mercer-Rosa, L.; Natarajan, S.S. Echocardiographic Screening of Cardiovascular Status in Pediatric Sickle Cell Disease. Pediatr. Cardiol., **2019**, 40, 1670–8.

[14] Ambrusko, S.J.; Gunawardena, S.; Sakara, A.; Windsor, B.; Lanford, L.; Michelson, P.; Krishnamurti, L. Elevation of Tricuspid Regurgitant Jet Velocity, a Marker for Pulmonary Hypertension in Children with Sickle Cell Disease. Pediatr. Blood Cancer, **2006**, 47, 907–13.

[15] Chinawa, J.M.; Chukwu, B.F.; Chinawa, A.T.; Ossai, E.N.; Ikefuna, A.N.; Aronu, A.E.; Obidike, E.O. Right Ventricular Function among South East Nigeria Children with Sickle Cell Anaemia. BMC Pediatr., **2020**, 20, 1.

[16] Colombatti, R.; Maschietto, N.; Varotto, E.; Grison, A.; Grazzina, N.; Meneghello, L.; Teso, S.; Carli, M.; Milanesi, O.; Sainati, L. Pulmonary Hypertension in Sickle Cell Disease Children Under 10 Years of Age: Pulmonary Hypertension in SCD Patients Under 10 Years Old. Br. J. Haematol., **2010**, 150, 601–9.

[17] Moher, D.; Liberati, A.; Tetzlaff, J.; Altman, D.G. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. Int. J. Surg., **2010**, 8, 336–41.

[18] Peterson, J.; Welch, V.; Losos, M.; Tugwell, P. The Newcastle-Ottawa scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses. Ottawa Hospital Research Institute, Ottawa, **2011**.

[19] Nyaga, V.N.; Arbyn, M.; Aerts, M.; Metaprop: A Stata Command to Perform Meta-Analysis of Binomial Data. Arch. Public Health, **2014**, 72, 39.

[20] Higgins, J.P.; Green, S. editors. Cochrane Handbook for Systematic Reviews of Interventions. John Wiley and Sons, United States, **2011**.

[21] Egger, M.; Smith, G.D.; Schneider, M.; Minder, C. Bias in Meta-Analysis Detected by a Simple, Graphical Test. BMJ, **1997**, 315, 629–34.

[22] Agha, H.; El Tagui, M.; El Ghamrawy, M.; Hady, M.A. The 6-Min Walk Test: An Independent Correlate of Elevated Tricuspid Regurgitant Jet Velocity in Children and Young Adult Sickle Cell Patients. Ann. Hematol., **2014,** 93, 1131–8.

[23] Cox, S.E.; Soka, D.; Kirkham, F.J.; Newton, C.R.; Prentice, A.M.; Makani, J.; Younoszai, A.K. Tricuspid Regurgitant Jet Velocity and Hospitalization in Tanzanian Children with Sickle Cell Anemia. Haematologica. **2014**, 99, e1.

[24] Dahoui, H.A.; Hayek, M.N.; Nietert, P.J.; Arabi, M.T.; Muwakkit, S.A.; Saab, R.H.; Bissar, A.N.; Jumaa, N.M.; Farhat, F.S.; Dabbous, I.A.; Bitar, F.F.; Abboud, M.R. Pulmonary Hypertension in Children and Young Adults with Sickle Cell Disease: Evidence for Familial Clustering. Pediatr. Blood Cancer, **2010**, 54, 398–402.

[25] Eddine, A.C.; Alvarez, O.; Lipshultz, S.E.; Lipshultz, S.E.; Kardon, R.; Arheart, K.; Swaminathan, S. Ventricular Structure and Function in Children with Sickle Cell Disease Using Conventional and Tissue Doppler Echocardiography. Am. J. Cardiol., **2012**, 109, 1358–64.

[26] Forrest, S.; Kim, A.; Carbonella, J.; Pashankar, F. Proteinuria is Associated with Elevated Tricuspid Regurgitant Jet Velocity in Children with Sickle Cell Disease. Pediatr. Blood Cancer, **2012**, 58, 937–40.

[27] Gordeuk, V.R.; Minniti, C.P.; Nouraie, M.; Campbell, A.D.; Rana, S.R.; Luchtman-Jones, L.; Sable, C.; Dham, N.; Ensing, G.; Prchal, J.T.; Kato, G.J.; Gladwin, M.T.; Castro, O.L. Elevated Tricuspid Regurgitation Velocity and Decline in Exercise Capacity over 22 Months of Follow up in Children and Adolescents with Sickle Cell Anemia. Haematologica, **2011**, 96, 33–40.

[28] Gore, S. Study of Prevalence of Pulmonary Hypertension in Children with Sickle Cell Anemia or Sickle Cell Disease. Joint Event Pediatr. Nutr. Prim. Healthc. Nurs., **2018**, 8, 42.

[29] Hagar, R.W.; Michlitsch, J.G.; Gardner, J.; Vichinsky, E.P.; Morris, C.R. Clinical Differences between Children and Adults with Pulmonary Hypertension and Sickle Cell Disease. Br. J. Haematol., **2017**, 140, 104-112

[30] Hebson, C.; New, T.; Record, E.; Oster, M.; Ehrlich, A.; Border, W.; James-Herry, A.; Kanaan, U. Elevated Tricuspid Regurgitant Velocity as a Marker for Pulmonary Hypertension in Children with Sickle Cell Disease: Less Prevalent and Predictive than Previously Thought? J. Pediatr. Hematol. Oncol., **2015**, 37, 134–9.

[31] Jesus-Rojas, W.; Mosquera, R.A.; DaCosta, C.; Stark, C.K.; Jon, K.; McBeth, A.; Yadav, A,; Houston, T.X. Screening of Pulmonary Hypertension in a Cohort of Children with Sickle Cell Disease. In: A62. Sickle Cell Disease. American Thoracic Society, New York, **2018**. pA2057.

[32] Lamina, M.O.; Animasahun, B.A.; Akinwumi, I.N.; Njokanma, O.F. Doppler Echocardiographic Assessment of Pulmonary Artery Pressure in Children with Sickle Cell Anaemia. Cardiovasc. Diag. Ther., **2019**, 9, 204–13.

[33] Liem, R.I.; Young, L.T.; Thompson, A.A. Tricuspid Regurgitant Jet Velocity is Associated with Hemolysis in Children and Young Adults with sickle Cell Disease Evaluated for Pulmonary Hypertension. Haematologica, **2007**, 92, 1549–52.

[34] Liem, R.I.; Nevin, M.A.; Prestridge, A.; Young, L.T.; Thompson, A.A. Tricuspid Regurgitant Jet Velocity Elevation and its Relationship to Lung Function in Pediatric Sickle Cell Disease. Pediatr. Pulmonol., **2009**, 44, 281–9.

[35] Minniti, C.P.; Sable, C.; Campbell, A.; Rana, S.; Ensing, G.; Dham, N.; Onyekwere, O.; Nouraie, M.; Kato, G.J.; Gladwin, M.T.; Castro, O.L.; Gordeuk, V.R. Elevated Tricuspid Regurgitant Jet Velocity in Children and Adolescents with Sickle cell Disease: Association with Hemolysis and Hemoglobin Oxygen Desaturation. Haematologica, **2009**, 94, 340–7.

[36] Molavi, M.A.; Rajaei, S.; Elahi, Z.; Nazemi, A.; Zare, S. Evaluation of Tricuspid Regurgitation Jet Velocity in Children with Sickle Cell Disease in Iran 2012-2013. Adv. Biores., **2015**, 6, 211.

[37] Mondal, P.; Stefek, B.; Sinharoy, A.; Sankoorikal, B.J.; Abu-Hasan, M.; Aluquin, V. The Association of Nocturnal Hypoxia and an Echocardiographic Measure of Pulmonary Hypertension in Children with Sickle Cell Disease. Pediatr. Res., **2019**, 85, 506–10.

[38] Nelson, S.C.; Adade, B.B.; McDonough, E.A.; Moquist, K.L.; Hennessy, J.M. High Prevalence of Pulmonary Hypertension in Children with Sickle Cell Disease. J. Pediatr. Hematol. Oncol.,

2007, 29, 334–7.

[39] Nouraie, M.; Darbari, D.S.; Rana, S.; Minniti, C.P.; Castro, O.L.; Luchtman-Jones, L.; Sable, C.; Dham, N.; Kato, G.J.; Gladwin, M.T.; Ensing, G.; Arteta, M.; Campbell, A.; Taylor, J.G 6th.; Nekhai, S.; Gordeuk, V.R. Tricuspid Regurgitation Velocity and Other Biomarkers of Mortality in Children, Adolescents and Young Adults with Sickle Cell Disease in the United States: The PUSH Study. Am. J. Hematol., **2020**, 95, 766–74.

[40] Onalo, R.; Cooper, P.; Cilliers, A.; Nnebe-Agumadu, U. Cardiovascular Changes in Children with Sickle Cell Crisis. Cardiol. Young, **2020**, 30, 162–70.

[41] Onyekwere, O.C.; Campbell, A.; Teshome, M.; Onyeagoro, S.; Sylvan, C.; Akintilo, A.; Hutchinson, S.; Ensing, G.; Gaskin, P.; Kato, G.; Rana, S.; Kwagyan, J.; Gordeuk, V.; Williams, J.; Castro, O. Pulmonary Hypertension in Children and Adolescents with Sickle Cell Disease. Pediatr. Cardiol., **2008**, 29, 309–12.

[42] Pashankar, F.D.; Carbonella, J.; Bazzy-Asaad, A.; Friedman, A. Prevalence and Risk Factors of Elevated Pulmonary Artery Pressures in Children with Sickle Cell Disease. Int. J. Contemp. Pediatr., **2008**, 121, 777–82.

[43] Patel, P.; Sharma, S.; Shah, N.; Manglani, M. Prevalence of Pulmonary Hypertension in Children with Sickle Cell Disease. Int. J. Contemp. Pediatr., **2016**, 3, 1076–82.

[44] Peter, I.D.; Asani, M.O., Abdullahi, S.U.; Aliyu, I.; Obaro, S.K.; Bode-Thomas, F. Pulmonary Hypertension and Right Ventricular Function in Nigerian Children with Sickle Cell Anaemia. Trans. R. Soc. Trop. Med. Hyg., **2019**, 113, 489–96.

[45] Qureshi, N.; Joyce, J.J.; Qi, N.; Chang, R.K. Right Ventricular Abnormalities in Sickle Cell Anemia: Evidence of a Progressive Increase in Pulmonary Vascular Resistance. J. Pediatr., **2006**, 149, 23–7.

[46] Sedrak, A.; Rao, S.P.; Miller, S.T.; Hekmat, V.; Rao, M. A Prospective Appraisal of Pulmonary Hypertension in Children with Sickle Cell Disease. J. Pediatr. Hematol. Oncol., **2009**, 31, 97-100.

[47] Sokunbi, O.J.; Ekure, E.N.; Temiye, E.O.; Anyanwu, R.; Okoromah, C.A.N. Pulmonary Hypertension among 5 to 18 Year Old Children with Sickle Cell Anaemia in Nigeria. PLoS One. **2017**, 12, e0184287.

[48] Suell, M.N.; Bezold, L.I.; Okcu, M.F.; Mahoney, D.H. Jr.; Bertuch, A.A. Increased Pulmonary Artery Pressures among Adolescents with Sickle Cell Disease. J. Pediatr. Hematol. Oncol., **2005**, 27, 654–8.

[49] Musa, B.M.; Galadanci, N.A.; Coker, M.; Bussell, S.; Aliyu, M.H. The Global Burden of Pulmonary Hypertension in Sickle Cell Disease: A Systematic Review and Meta-Analysis. Ann. Hematol., **2016**, 95, 1757–64.

[50] Bigna, J.J.; Noubiap, J.J.; Nansseu, J.R.; Aminde, L.N. Prevalence and Etiologies of Pulmonary Hypertension in Africa: A Systematic Review and Meta-Analysis. BMC Pulm. Med., **2017**, 17, 183.

[51] Bigna, J.J, Nansseu, J.R.; Noubiap, J.J. Pulmonary Hypertension in the Global Population of Adolescents and Adults Living with HIV: A Systematic Review and Meta-Analysis. Sci. Rep., **2019**, 9, 7837.

[52] Schoenberg, N.C.; Argula, R.G.; Klings, ES.; Wilson, K.C.; Farber, H.W. Prevalence and Mortality of Pulmonary Hypertension in ESRD: A Systematic Review and Meta-Analysis. Lung. **2020**, 198, 535–45.

[53] Avouac, J.; Airò, P.; Meune, C.; Beretta, L.; Dieude, P.; Caramaschi, P.; Tiev, K.; Cappelli, S.; Diot, E.; Vacca, A.; Cracowski, J.L.; Sibilia, J.; Kahan, A.; Matucci-Cerinic, M.; Allanore, Y. Prevalence of Pulmonary Hypertension in Systemic Sclerosis in European Caucasians and Meta-Analysis of 5 Studies. J. Rheumatol., **2010**, 37, 2290–8.

[54] Rhodes, C.J.; Wharton, J.; Wilkins, M.R. Pulmonary Hypertension: Biomarkers. Handb. Exp. Pharmacol., **2013**, 218, 77–103.

Publisher's note