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Factors associated with left ventricular hypertrophy in children with sickle cell disease; results from the DISPLACE study

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Author Contributions
Dr. Galadanci drafted the initial manuscript and reviewed and revised the manuscript. Drs. Galadanci, Johnson, Howard and Kanter conceptualized and designed the study. Dr Galadanci and Gerhard collected and analyzed the data. All authors drafted the initial manuscript, reviewed, and revised the manuscript and approved the submitted version.
ABSTRACT

Cardiopulmonary complications remain a leading cause of morbidity and mortality in sickle cell disease (SCD). The overall goals of this study were to evaluate the relationship between left ventricular hypertrophy (LVH) and laboratory markers of hemolysis and determine the association between LVH and SCD-specific therapies (Hydroxyurea and Chronic red cell transfusion). Data from DISPLACE (Dissemination and Implementation of Stroke Prevention Looking at the Care Environment) study cohort was used. LVH was defined based on the left ventricular mass indexed to the body surface area as left ventricular mass index > 103.0 g/m\(^2\) for males and >84.2 g/m\(^2\) for females.

There were 1409 children included in the analysis and 20.3% had LVH. Results of multivariable analysis of LVH showed baseline hemoglobin levels were associated with the lower odds of having LVH (OR: 0.71, 95% CI: 0.60 – 0.84). The odds of LVH increases for every one-year increase in age (OR: 1.07, 95%CI: 1.02-1.13). Similarly, the odds of LVH were lower among males than females (OR: 0.59, 95%CI: 0.38-0.93). The odds of LVH were higher among those on hydroxyurea compared to no therapy (OR: 1.83, 95% CI: 1.41 – 2.37). Overall results of the study showed that LVH occurs early in children with SCD and the risk increases with increasing age and with lower hemoglobin. Further, we found higher use of hydroxyurea among those with LVH, suggesting that the need for hydroxyurea conveys a risk of cardiovascular remodeling.
INTRODUCTION

Improvements in healthcare and disease management have allowed more children with sickle cell disease (SCD) to reach adulthood, increasing the need to prevent disease-specific complications. Cardiopulmonary complications remain a leading cause of morbidity and mortality in SCD, particularly for people with sickle cell anemia (SCA) who have lower hemoglobin and higher baseline rate of hemolysis.

Children with SCA frequently have severe anemia that results in increased cardiac output and cardiac dilatation corresponding to hemoglobin (Hb) level. The dilated left ventricle adapts partially by hypertrophy, initially preserving diastolic compliance and maintaining the filling pressure at normal levels. Ultimately, these adaptive responses may become maladaptive, resulting in left ventricular diastolic and systolic dysfunction. Data suggest that left ventricular hypertrophy (LVH) may be the first step in the development of pulmonary hypertension in patients with SCA. But the time course and mechanisms by which LVH may progress to pulmonary hypertension are not well understood.

In 2014, the American Thoracic Society recommended all adults with SCD receive screening echocardiography and that those with TRJV $\geq 2.5$ m/sec receive hydroxyurea therapy (HU) or chronic red cell transfusion therapy (CRCT) for those patients who are not eligible for HU. However, the recommendations were solely
based on the overall beneficial effects of HU and CRCT in individuals with SCD and not due to the direct effect of these therapies on cardiopulmonary complications. In contrast, the American Society of Hematology cardiopulmonary-renal guidelines published in 2020 recommended screening echocardiography only in those adults with SCD who presented with cardiopulmonary symptoms such as dyspnea on exertion, chest pain, pedal edema, or other manifestations of complications.¹⁵

There are no current recommendations on cardiopulmonary screening of children with SCD. Further, there are minimal data on which children with SCD will develop cardiopulmonary complications and if there are early biomarkers in these children that can be monitored for cardiac disease progression. Thus, while many children with SCD undergo echocardiography, there are no standard recommendations for initial or follow-up screening.

The DISPLACE (Dissemination and Implementation of Stroke Prevention Looking at the Care Environment) study, is an NHLBI funded study to evaluate the real-world use of transcranial Doppler (TCD) screening and stroke prevention in children with SCA from 28 clinical centers in the US.¹⁶ Data collected included laboratory assessments, echocardiography reports, Transcranial Doppler ultrasound (TCD) reports, and brain magnetic resonance imaging (MRI) reports. Using data from the DISPLACE study, the overall goals of this analysis were to determine the prevalence of LVH in children with SCD, evaluate the relationship between LVH and laboratory markers of hemolysis, and determine the association between LVH and SCD-specific therapies (HU and CRCT).
METHODS

Study population and design

This study was conducted as a cross-sectional study using data collected as part of the DISPLACE study.\textsuperscript{16} The DISPLACE study collected data on 5,247 children with SCD aged 2-19 years from 28 centers in the US with multiple years of consecutive data.\textsuperscript{16} DISPLACE focused on obtaining data of children between the ages of 2 and 16 years during the initial retrospective assessment to determine the frequency of TCD screening for stroke prevention. Data were collected from the clinical records of the children with a focus on clinical data from 2012-2016 but included all radiographic data (including echocardiograms and brain imaging) that were available throughout the child's lifespan (including a range of 2000 to 2020). The echocardiograms were performed according to institutional standard of care (i.e., outside of DISPLACE) and interpreted according to American Society of Echocardiography guidelines. This study used echocardiogram reports only (i.e., images were not reviewed) and a statistical program was used for data abstraction and entry to standardize echocardiogram data across all centers.

Data collected included vital signs (heart rate, blood pressure, height and weight), laboratory tests including complete blood count and reticulocyte count, and use of SCD-related therapies (CRCT and HU). The inclusion criteria for this study were (1) available echocardiographic results and (2) available clinical and laboratory tests during the same year as the echocardiogram. Children who did not have at least one echocardiogram or at least one set of laboratory and clinical assessments were excluded. Additionally, although the DISPLACE study included longitudinal data on
each patient (i.e., multiple records per patient); however, each patient’s data was only included once in the current analysis.

_Institutional Review Board and Data Use Agreements._

Institutional Review Board (IRB) approval and data use agreement for the DISPLACE study were obtained at and between each clinical institution and the sponsoring institution using a common protocol. All data were de-identified at time of entry and all data was retrospective; thus, consent was not required from individual patients or their families. For the current analysis, we further obtained IRB approval from the University of Alabama at Birmingham to evaluate the de-identified data.

_Variables_

Our primary outcome was LVH defined as left ventricular mass index >95th percentile. The left ventricular mass index was calculated by dividing the left ventricular mass by the body surface area and defined based on sex. LVH was therefore defined as left ventricular mass index > 103.0 g/m² for males and >84.2 g/m² for females.17

Our predictor variables included the available measurements of hemolysis (hemoglobin and reticulocyte count) and the SCD medication use (ever use of HU or CRCT versus never). Our covariates included age, sex (male or female), systolic blood pressure, diastolic blood pressure, heart rate, height, weight, history of overt ischemic stroke as defined by the MRI and clinical history. Selection of variables was based on previous literature.18, 19 These variables were identified by chart review as part of the DISPLACE study, and adherence to HU or CRCT was not evaluated for this study.

For those children with multiple echocardiographs, we used only one assessment and the corresponding clinical and laboratory values from that same year. Additionally,
all complete blood count (CBC) tests for the DISPLACE study were taken at steady state, free from transfusion within the prior month. For children with more than one CBC test in a year, we used the results of CBC that was taken close to the date of the echocardiogram.

Statistical Analysis

Descriptive analysis was carried out to examine the association between predictor variables with LVH. Median and interquartile range (IQR) were reported for age, hemoglobin level, reticulocyte count, height, weight, heart rate, systolic blood pressure, and diastolic blood pressure, whereas frequencies and percentages were reported for sex, history of stroke, HU, and CRCT. In the bivariate analysis, Kruskal-Wallis test and Cochran-Mantel-Haenszel test were conducted for continuous and categorical variables, respectively.

To determine the association between the hemolytic measurements-hemoglobin and reticulocyte count and LVH, logistic regression models were fit to obtain odds ratios (OR) and 95% confidence intervals (CI) for LVH. The first model was adjusted for age and sex. The second model included additional adjustment for blood pressure, heart rate, height, weight, and history of stroke.

Further, to determine the association between SCD therapy and LVH, a logistic regression was fit and adjusted for age, sex, systolic and diastolic blood pressure, heart rate, height, weight, and history of stroke. Using the no therapy group as the reference group, adjusted ORs with their accompanying CIs were calculated for CRCT and HU groups. We fitted two models, first model without Hemoglobin and reticulocyte (not included in the model since they are directly impacted by both HU and CRCT. In a
second model, we forced hemoglobin into the model to see how it will amplify the effect of the treatment.

All reported P values were 2-sided. Statistical significance was defined as $p < 0.05$. All data analysis were performed using SAS 9.4, (SAS Institute, Cary, NC).

RESULTS

Participants’ characteristics at baseline

Demographic, laboratory, and clinical characteristics of children are shown in table 1. A total of 1409 children with SCD from the DISPLACE database were included in the analysis. (Figure 1) All the children had SCA (HbSS or HbSB0). All children had at least one documented echocardiogram entered in the DISPLACE database.

Of the 1409 children, 20.3% had LVH. (Table 1). There were no differences in sex, systolic blood pressure, z-score for weight, diastolic blood pressure and reticulocyte count between those with and without LVH. (Table 1). Children who had LVH had a significantly lower hemoglobin level ($p<0.0001$) compared to those without LVH. Similarly, children who had LVH were older ($p = 0.0006$), had a lower z-score for height ($p=0.0121$) and lower heart rate ($p<0.0001$). A lower proportion of children with LVH were on CRCT compared to children without LVH, while a higher proportion of children with LVH were on hydroxyurea compared to no LVH ($p < 0.0001$).

Predictors for LVH in children with SCD

Hemoglobin was significantly associated with the odds of having LVH (OR: 0.71, 95% CI: 0.60 – 0.84). The odds of LVH were lower per 1g increase in hemoglobin. This association remained significant after multivariable adjustments in the sequential
models. (Table 2). The difference among the LVH group for reticulocyte was not statistically significant, (OR: 0.99, 95% CI: 0.99-1.00) and the association remained the same after adjustment. The odds of LVH increases for every one-year increase in age (OR: 1.07, 95%CI: 1.02-1.13). Similarly, the odds of LVH was lower among males than females (OR: 0.59, 95%CI: 0.38-0.93). There was no evidence that the odds of LVH was significantly associated with any of the other covariates. (Table 2).

Association between SCD therapies and LVH

For the analysis between SCD therapies and LVH, children who had not received any disease modifying therapy or those treated with either HU or CRCT were included (n =1250). Assessments of adherence to disease modifying-therapy was beyond the scope of this analysis. We excluded children who were on both HU and CRCT (n=108). Compared to those not on either therapy, HU was significantly associated with LVH. The odds of LVH were higher among those on HU compared to no therapy (OR: 1.83, 95% CI: 1.41 – 2.37), and this association remained significant after multivariable adjustment. When we forced hemoglobin into the model, we found the odds of LVH were higher among those on HU compared to no therapy, but the association was not statistically significant. We found no significant association between CRCT and LVH. (Table 3).

DISCUSSION

In this large retrospective analysis of children with SCD, the prevalence of LVH was 20% and was associated with lower hemoglobin and HU use. Previous studies including a meta-analysis reviewing studies of left ventricular systolic dysfunction in
SCD have shown that LVH is a common finding in individuals with SCD.\textsuperscript{19-21} Most of these earlier analyses found an even higher prevalence of LVH of 25\% to 40\%. These findings were likely due to the inclusion of older age groups which have an increased prevalence of LVH. Additionally, most of these studies included a comparison group of individuals without sickle cell disease.

As shown in the multivariable adjusted model, the odds of having LVH was higher among those with lower hemoglobin level. Our results are consistent with previous studies that also showed increased anemia (measured by hemoglobin) was associated with increased cardiopulmonary complications including LVH.\textsuperscript{21} Though we found no significant association between LVH and reticulocyte count, there was more missing data on reticulocyte count in this limiting the investigation.

As expected, age was significantly associated with LVH. This was consistent with findings from previous studies showing increasing left ventricular mass with increasing age.\textsuperscript{20} This study had a lower median age for LVH than reported in previous studies, possibly due to the fact that most studies were conducted on samples including children and adults while this study was solely focused on children <19 years. The youngest patient in this cohort with LVH was 9 years. The likelihood of LVH was found to increase roughly about 10\% for every year of age.

It is unclear how the development of LVH relates to or predates other cardiovascular complications in SCD. The most prominent identified risk factor for death in adults with SCD is an elevated TRJV $\geq 2.5$ m/sec.\textsuperscript{2} Other studies have shown that other cardiopulmonary complications in SCD are associated with death including myocardial infarction, chronic heart failure, arrhythmias and pulmonary hypertension.\textsuperscript{22}
These studies also identified worsened anemia in SCD is associated with increased risk for early death. Although children may have an elevated TRJV, studies have not found an association between premature mortality and high TRJV in children. However, it will be important to identify whether other cardiac abnormalities seen in children can predict the development of pulmonary hypertension. Other abnormalities/changes seen in the echocardiogram including LVH in children may be associated with progressive cardiopulmonary disease. A comprehensive prospective study is needed to determine which children with SCD are the greatest risk for cardiopulmonary complications in order to identify potential novel therapies that could be initiated in childhood for those individuals.

Our results showed a significantly higher odds of LVH among females than males. We used a gender-based definitions of LVH as previously published by Daniels et al in which the left ventricular mass was corrected for body surface area as required in children. The results of their study showed that despite correcting for body surface area in children, the left ventricular mass still differs by gender and therefore recommended that left ventricular mass should be corrected for both body surface area and gender in children. Similarly, this same recommendation was made in recent studies. And as highlighted by Sethna and Leishman 2016, there is no clear consensus among specialists performing echocardiograms and clinicians on the definition of LVH in children including indexing method, and therefore we chose to use the most conservative approach within the limit of data available to us.
In the current study, we found a significant association between LVH and HU but no association between LVH and CRT. Children on HU had a significantly higher odds of LVH compared to those on no therapy. This is in contrast to findings from previous studies in adults that showed HU was associated with a decreased risk of cardiopulmonary abnormalities and other comorbidities.\textsuperscript{12, 19, 23} Specifically, results from a small study of adults with SCD in Brazil, showed that patients taking HU were less likely to have LVH than those not taking the medication.\textsuperscript{19}

Previous studies in adults have shown no difference in tricuspid regurgitation velocity in those receiving hydroxyurea compared with those not receiving hydroxyurea.\textsuperscript{28, 29} While others showed no evidence of protective effect of hydroxyurea on pulmonary hypertension.\textsuperscript{29, 30} Although there is no direct evidence of a beneficial effect of HU on pulmonary hypertension, the American Thoracic Society guidelines recommend that all adults with SCD and pulmonary hypertension receive HU, and for those in whom HU is contraindicated, that they should receive CRCT.\textsuperscript{14} This is solely based on the direct benefit of HU and CRCT on morbidities in SCD and studies were correlative.

More recently the results of a retrospective longitudinal analysis of echocardiograms in patients with SCD, the authors found a high prevalence of LVH among patients on hydroxyurea, with higher prevalence among those treated for less than a year than those who had been treated longer.\textsuperscript{31} Further in the same study, analysis of serial echocardiogram reports showed that left ventricular dilation and hypertrophy improved significantly with hydroxyurea treatment, with a negative correlation between the treatment duration and left ventricular volume and mass.\textsuperscript{31}
Interestingly, our results differed from these expectations and findings, and did not support the initial hypothesis that HU would be protective against LVH. However, our study is limited as a cross-sectional analysis without the ability to evaluate children prospectively or to evaluate HU adherence. Considering HU may have been prescribed to children with more severe SCD including those with recurrent severe vasoocclusive crises, chronic anemia, and severe acute chest syndrome, it may be that this finding was a marker of disease severity as opposed to a medication effect. In other words, our finding of higher HU use among those with LVH, may be strongly associated with the fact that incidentally, those children on HU are the same children that are more likely to have more severe disease and at risk of other sickle cell complications and therefore likely to develop LVH. Future prospective studies will be targeted at specifically following our cohort of children to determine if been on HU indeed protects against worsening LVH or the development of other cardiopulmonary findings.

As expected with a retrospective study design, this study has limitations. DISPLACE is a real-world evaluation of current practice in clinical centers in the US. Most of these centers were academic centers, which may bias the sample, but generally in the U.S, majority of children with SCD attend clinic at academic institutions. Additionally, 3000 children without an echocardiograph were excluded from the current analysis. Therefore, to ensure our study population did not differ from the original DISPLACE study, we compared the baseline characteristics of the participants included in our analysis to the general DISPLACE participants and we found no significant difference in the baseline demographic and laboratory characteristics between the two population. (Supplemental table 1). Additionally, we used only available data and
therefore were not able to include other important hemolytic factors like lactate dehydrogenase. Furthermore, we were not able to confirm the protective effect of HU on LVH as we didn’t prospectively follow the patients to determine if indeed HU protects against LVH. Additionally, we were not able to include data on alpha thalassemia of our study participants despite its role in many cardiovascular complications of sickle cell disease. As mentioned in the methods section, our study design was a retrospective crossectional design and therefore we used only data that was available in the DISPLACE database. Alpha thalassemia was not collected in this database.

The strengths of our study include the use of a large national population sample of children with SCD from 28 sites across the US, which therefore improves the precision of our results and facilitates the generalizability of our findings. In addition, our study provides pertinent information to support initiating echocardiographic screening at an earlier age and the need to investigate for other cardiopulmonary markers of morbidity in children than currently practiced.

CONCLUSION

Our study showed that LVH occurs at an early age in some children with SCD and the risk increases with increasing age and with lower hemoglobin. Our results showed no indication of a causal relationship between HU and LVH. We found higher use of HU among those with LVH, suggesting that children with severe form of the disease requiring HU are also at increased risk of cardiovascular remodelling. Our findings suggest that we need to identify whether LVH or other echocardiography findings could be used as a biomarker for long-term cardiovascular complications in SCD. Future studies should target identifying earlier cardiopulmonary markers of morbidity and
potential therapies (including stem cell transplant) that could be initiated early in childhood for the most at-risk individuals.
REFERENCES

Table 1. Demographics and clinical characteristics of children with sickle cell disease comparing those with left ventricular hypertrophy to those without

<table>
<thead>
<tr>
<th>Variables</th>
<th>N</th>
<th>#Left Ventricular Hypertrophy</th>
<th><strong>P-value</strong></th>
<th>#No Left Ventricular Hypertrophy</th>
<th><strong>P-value</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>1409</td>
<td>286 (20.3)</td>
<td></td>
<td>1123 (79.7)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Age in years</td>
<td>1403</td>
<td>9.1 ± 4.4</td>
<td></td>
<td>8.2 ± 4.8</td>
<td></td>
</tr>
<tr>
<td>Sex, n(%)*</td>
<td></td>
<td></td>
<td>0.2949</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>725</td>
<td>209 (49.2)</td>
<td></td>
<td>516 (52.3)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>685</td>
<td>215 (50.1)</td>
<td></td>
<td>470 (47.7)</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>950</td>
<td>8.3 (7.6, 9.2)</td>
<td>&lt;0.0001</td>
<td>8.9 (8.0, 9.9)</td>
<td>0.9391</td>
</tr>
<tr>
<td>Reticulocyte count (per 1000)</td>
<td>637</td>
<td>290 (109, 411)</td>
<td></td>
<td>280 (161, 386)</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>642</td>
<td>110 (102, 117)</td>
<td>0.0739</td>
<td>108 (100, 116)</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>642</td>
<td>61 (56, 67)</td>
<td>0.7182</td>
<td>63 (56, 68)</td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>842</td>
<td>86 (77, 98)</td>
<td>&lt;0.0001</td>
<td>92 (83, 106)</td>
<td></td>
</tr>
<tr>
<td>Z-score for weight</td>
<td>1090</td>
<td>-0.29 (-1.13, 0.43)</td>
<td>0.2292</td>
<td>-0.26 (-0.99, 0.51)</td>
<td></td>
</tr>
<tr>
<td>Z-score for Height</td>
<td>1047</td>
<td>-0.43 (-1.14, 0.33)</td>
<td>0.0128</td>
<td>-0.18 (-1.00, 0.49)</td>
<td></td>
</tr>
<tr>
<td>History of stroke, n(%)</td>
<td>1409</td>
<td>25 (5.9)</td>
<td>0.2102</td>
<td>77 (7.8)</td>
<td></td>
</tr>
<tr>
<td>Therapy group, n(%)</td>
<td>1250</td>
<td>51 (12.0)</td>
<td>&lt;0.0001</td>
<td>139 (14.0)</td>
<td></td>
</tr>
<tr>
<td>Chronic Red Cell Transfusion</td>
<td>190</td>
<td>183 (43.1)</td>
<td></td>
<td>311 (31.4)</td>
<td></td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>494</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No therapy</td>
<td>617</td>
<td>150 (35.4)</td>
<td></td>
<td>467 (47.2)</td>
<td></td>
</tr>
</tbody>
</table>

Variables are reported as median (interquartile range)
*Variables are reported as the frequency and percent relative to the row attribute
**P-values from Row mean zero scores differ using Cochran-Mantel-Haenszel test for categorical and Wilcoxon rank sum test for continuous variables

# Left ventricular hypertrophy: Left ventricular mass index > 103.0 g/m² for males, Left ventricular mass index > 84.2 g/m² for females

#No LVH: Left ventricular mass index <= 103 g/m² for males, Left ventricular mass index <= 84.2 g/m² for females
Table 2. **Odds ratios and 95% confidence interval for the association between hemolytic factors and left ventricular hypertrophy in children with sickle cell Disease**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Model 1</th>
<th></th>
<th>Model 2</th>
<th></th>
<th>Model 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P value</td>
<td>OR (95% CI)</td>
<td>P value</td>
<td>OR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>0.79 (0.70 – 0.93)</td>
<td>0.0054</td>
<td>0.76 (0.64-0.90)</td>
<td>0.0020</td>
<td>0.78 (0.66-0.94)</td>
<td>0.0072</td>
</tr>
<tr>
<td>Reticulocyte count</td>
<td>1.00 (0.99-1.00)</td>
<td>0.5080</td>
<td>1.00 (0.99-1.00)</td>
<td>0.7476</td>
<td>1.00 (1.00-1.00)</td>
<td>0.8223</td>
</tr>
<tr>
<td>Age (years)</td>
<td>-</td>
<td>-</td>
<td>1.07 (1.02-1.13)</td>
<td>0.0061</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Male sex</td>
<td>-</td>
<td>-</td>
<td>0.59 (0.38, 0.93)</td>
<td>0.0214</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Heart rate beats/min</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.98 (0.97-1.00)</td>
<td>0.0468</td>
</tr>
<tr>
<td>Systolic blood pressure (mmhg)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.00 (0.98-1.02)</td>
<td>0.8631</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmhg)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.01 (0.98-1.04)</td>
<td>0.4920</td>
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<tr>
<td>Z score Weight</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.03 (0.77-1.38)</td>
<td>0.1799</td>
</tr>
<tr>
<td>Z score Height</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.81 (0.60-1.10)</td>
<td>0.8378</td>
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<tr>
<td>Stroke history</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.43 (0.51-4.03)</td>
<td>0.5013</td>
</tr>
</tbody>
</table>

Logistic regression was used to calculate odds ratio for the association between hemolytic factors and left ventricular hypertrophy. **Model 1 was unadjusted, model 2 was adjusted for age and sex, Model 3 was adjusted for heart rate, history of stroke, systolic blood pressure, diastolic blood pressure, z score for weight and z score for height.**
Table 3. Crude and Adjusted odds ratios** and associated 95% Confidence intervals (95%CI) for the association between sickle cell disease therapy and left ventricular hypertrophy

<table>
<thead>
<tr>
<th></th>
<th>++No Sickle Cell Disease Therapy</th>
<th>Hydroxyurea</th>
<th>Chronic Red Cell Transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number (%)</strong></td>
<td>617 (494)</td>
<td>494</td>
<td>139</td>
</tr>
<tr>
<td><strong>Number with LVH (%)</strong></td>
<td>150 (35.4)</td>
<td>183 (43.1)</td>
<td>51 (12.0)</td>
</tr>
<tr>
<td><strong>Crude odds ratio (95% CI)</strong></td>
<td>1.0 (ref)</td>
<td>1.83 (1.41-2.37)</td>
<td>1.14 (0.79 – 1.65)</td>
</tr>
<tr>
<td>*Adjusted odds ratio (95% CI)</td>
<td>1.0 (ref)</td>
<td>1.51 (1.02-2.22)</td>
<td>0.62 (0.25 – 1.53)</td>
</tr>
</tbody>
</table>

Abbreviations N (%) - Number (percent); Percent represent percent of those in each therapy group among total with LVH CI - Confidence interval, LVH - Left Ventricular Hypertrophy

**Logistic regression was used to calculate odds ratio for LVH comparing therapy groups. *adjusted for age, sex, heart rate, history of stroke, systolic blood pressure, diastolic blood pressure, weight and height. ++The reference group is the group on no therapy.

Figure 1. Flow chart depicting the number of DISPLACE study participants included in the analysis
5,247 children in the DISPLACE cohort

3,838 excluded due to no available echo result and missing labs

1,409 children included in the analysis

286 Children with left ventricular hypertrophy

1,123 children without left ventricular hypertrophy

DISPLACE: Dissemination and Implementation of Stroke Prevention Looking at the Care Environment
Supplemental Table 1: Baseline demographic, clinical and laboratory characteristics of the DISPLACE cohort comparing children who were included in the Echocardiographic study and those excluded.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number</th>
<th>Echocardiogram</th>
<th>No echocardiogram</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>5428</td>
<td>1412 (26.0)</td>
<td>4016 (73.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age*</td>
<td>3480</td>
<td>8.5±4.5</td>
<td>5.8±4.5</td>
<td></td>
</tr>
<tr>
<td>Sex, n(%)*</td>
<td></td>
<td></td>
<td></td>
<td>0.2886</td>
</tr>
<tr>
<td>Male</td>
<td>2724</td>
<td>725 (51.4)</td>
<td>1999 (49.8)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2702</td>
<td>685 (48.6)</td>
<td>685 (48.5)</td>
<td></td>
</tr>
<tr>
<td>Race, n(%)*</td>
<td></td>
<td></td>
<td></td>
<td>0.3325</td>
</tr>
<tr>
<td>Black</td>
<td>5142</td>
<td>1332 (95.7)</td>
<td>3810 (95.0)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>67</td>
<td>21 (1.5)</td>
<td>46 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>16</td>
<td>1 (0.1)</td>
<td>15 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>194</td>
<td>53 (3.8)</td>
<td>141 (3.5)</td>
<td></td>
</tr>
<tr>
<td>Insurance, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.4758</td>
</tr>
<tr>
<td>Medicaid</td>
<td>2498</td>
<td>756 (71.8)</td>
<td>1742 (70.5)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>973</td>
<td>285 (27.1)</td>
<td>688 (27.9)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>52</td>
<td>12 (1.1)</td>
<td>40 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dl)†</td>
<td>3258</td>
<td>8.7 (7.8, 9.6)</td>
<td>8.6 (7.8, 9.5)</td>
<td>0.3598</td>
</tr>
<tr>
<td>Reticulocyte count (per 1000)†</td>
<td>2011</td>
<td>297.0 (194.4, 408.0)</td>
<td>295.0 (191.0, 349.0)</td>
<td>0.4696</td>
</tr>
</tbody>
</table>

Abbreviations: n(%) - number(percent), † value reported is median and Interquartile range, # value reported is mean ± 2standard deviation, * value reported is frequency and percentage of total.