Lung Function Abnormalities in Sickle Cell Anaemia

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Weight, BMI, mean FVC, and FEV1% predicted values were comparatively lower among the Hb-SS patients (p < 0.001). Abnormal spirometry outcome occurred in 70.4% of Hb-SS patients, predominantly restrictive defects (p < 0.001), and showed no significant association with steady-state Hb, WBC count, free plasma haemoglobin, frequency of sickling crisis, chronic leg ulcers, and TRV measurements (p > 0.05). The mean oxygen saturation was comparatively lower among Hb-SS patients (p < 0.001).

Conclusion. Measured lung volumes were significantly lower in Hb-SS patients when compared to non-SCD controls and this difference was not influenced by anthropometric variance. Lung function abnormalities, particularly restrictive defects, are prevalent in Hb-SS patients but showed no significant association with recognized markers of disease severity.

1. Introduction

The lung is one of the major organs affected by sickle cell disease (SCD) being a common site of hypoxic and ischaemic injury and emboli from marrow infarcts/fat necrosis and is plagued with increased propensity for developing pneumonias [1–3]. Acute and chronic lung complications in sickle cell disease are major causes of morbidity and mortality, accounting for 20-30% of all sickle cell deaths [1, 4]. Chronic complications could manifest as abnormalities in lung function, interstitial lung disease, or pulmonary hypertension. Lung function abnormalities have been shown to commonly occur in a majority of SCD patients even at steady state and these include lower lung volumes (FEV1/FVC), decreased diffusion capacity for carbon monoxide, airway hyperresponsiveness/asthma, and hypoxaemia [5, 6]. The reported prevalence of these lung function abnormalities is varied [7–11]. Although early stages of these lung function abnormalities are usually asymptomatic, a significant number of SCD patients may have dyspnoea on exertion with reduced exercise capacity when severe [12]. A recent study found an association between low FEV1 and increased risk of mortality among adults with Hb-SS [13]. Powars et al. had earlier suggested that abnormalities in lung function tests could be
the first objective sign of sickle cell chronic lung disease and
could reduce morbidity when detected early through screen-
ing [10]. The current study therefore sought to determine the
prevalence and pattern of lung function abnormalities among
a cohort of adult Hb-SS patients compared to healthy non-
SCD controls and identify associated factors.

2. Methods

This was an analytical cross-sectional study carried out
between March and June 2014. The study was conducted
at the Ghana Institute of Clinical Genetics which houses
the sickle cell clinic of the Korle-Bu Teaching Hospital,
a major referral site for the Accra Metropolis. The study
sample consisted of 76 randomly selected Hb-SS adults, 18
years and above from the out-patient unit of the sickle
cell clinic who were in their steady state with results of
electrophoresis clearly documented in their medical records.
Seventy-six-year-old and sex matched non-SCD controls
were selected from among the healthcare staff of the above
hospital.

A structured questionnaire was used to collect partici-
pants’ sociodemographic and medical information after writ-
ten consent was obtained. Anthropometric measurements
such as weight, height, and BMI were taken as well as blood
pressure, pulse rate, and oxygen saturation using Omron
digital BP machine (Intelli Sense R) and ChoiceMMED
brand pulse oximeter, respectively. A modified version of St.
George's Respiratory questionnaire was used to screen the
participants for symptoms of chronic respiratory diseases and
excluded if present. General cardiorespiratory examination
was performed on all participants to further exclude res-
piratory, cardiovascular, and musculoskeletal abnormalities
that were capable of influencing the spirometry or echocar-
diogram results. Spirometry was performed and interpreted
for all participants according to American Thoracic Society
(ATS) protocol using SCHILLER SPIROVIT SP-1 (Schiller-
AG, Switzerland) [14]. The best of three FEV1 and FVC
test value from acceptable and reproducible maneuvers was
recorded as both absolute and percentage predicted values.
Abnormal FEV1 or FVC% predicted was defined as values <
80% of predicted values. For the purposes of this research,
a forceful blow of ≥ 3sec was considered an acceptable blow
for interpretation and analysis [9]. Blood samples taken were
analysed for complete blood count, urea, and creatinine
and free plasma haemoglobin (a marker of intravascular
haemolysis). For the latter, solid phase-phase sandwich ELISA
technique was used and optimization was predetermined
prior to running the test sample. Values >40μg/ml were
regarded as abnormal and suggestive of ongoing intravascular
haemolysis [3]. Patients underwent transthoracic echocar-
diogram which was performed by a consultant cardiologist
using a Toshiba brand ECHO machine, Apio 300 3MHz
transducer in accordance with the American echocardiog-
raphy society guidelines [15]. The average of three different
TRV measurements was recorded as the mean TRV value,
where values ≥ 2.5m/s were classified as elevated TRV
[16].

2.1. Study Definitions. Steady state: absence of acute painful
events or hemolytic episodes 4 weeks prior to recruitment as
well as no hemotransfusion within the same specified period.
Sickle cell crisis: sickle cell crisis was defined as acute
painful episodes that required use of oral or intravenous
analgesics and led to ER or daycare visits with or without
hospitalization.

Severity of disease: for the purpose of this study disease
severity was defined as (1) having 3 or more acute painful
episodes in the past one year prior to study [17]; (2) history
of chronic leg ulcer (3) history of priapism; (4) elevated TRV
on ECHO.

Data analysis was done using Statistical Package for
Social Sciences (SPSS) version 22. ANOVA was used to
compare FVC and FEV1% predicted values among the
study participants as well as comparing means of labora-
tory indices between Hb-SS participants with normal and
abnormal spirometry outcomes. Spearman’s rank correlation
and Dunnet’s pairwise post hoc analysis were used to
establish relationships between spirometry and laboratory
measurements. Chi-square test was employed to compare
proportions of spirometry outcomes among relevant cate-
gories of respondents. Linear regression and multivariate
analysis were used to examine significant factors influencing
spirometry outcomes.

Approval was obtained from the Ethical and Protocol
Review Committee of the College of Health sciences, Univer-
sity of Ghana (protocol identification number CHS-Et/M.10-

3. Results

Table1 shows the age and gender distribution as well as
anthropometric characteristics of the participants. The mean
age for the Hb-SS participants was 33.8 ± 11.1 years with
majority (60.5%) being females. The mean weight and BMI of
Hb-SS participants were 59±13.2kg and 21.8±4.2, respectively,
compared to 69.1± 14.5kg and 25.1± 4.8, respectively, among
the controls (p < 0.001). Both groups had comparable mean
height of 164.3± cm and 166.1 ± cm, respectively (p = 0.077).

participants, 6 (7.9%) had associated hypertension, only 1
(1.3%) had diabetes, and 1(1.3%) had chronic kidney dis-
ease (CKD). Fifty-three (69.7%) had a history of previous
blood transfusion and 28 (36.8%) had a history of chronic
(present/past/recurrent) leg ulcers. Nine (25.7%) out of the
30 males had a previous history of priapism, mostly in the
adolescent period. Sixty-three (82.9%) had at most 2 episodes
of vasooclusive (VOC) crisis in the year prior to the study,
while 13 (17.1%) had 3 or more episodes over the past year.

3.2. Lung Function Parameters of Hb-SS Compared to Non-
SCD Controls. Five Hb-SS participants and 2 of the controls
had poor spirometry tests (forceful blow duration less than
3secs); thus their results were not included in the analysis.
From Table 1, the mean FVC and FEV1% predicted of the Hb-
SS patients were 72.6 ± 22.2% and 65.3 ± 20.6%, respectively,
Table 1: Demographic characteristics and lung function parameters of participants.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hb-SS subjects</td>
<td>76</td>
<td>59.00</td>
<td>13.20</td>
<td>38.00</td>
<td>117.50</td>
<td>&lt;0.001</td>
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<td>Controls</td>
<td>76</td>
<td>69.10</td>
<td>14.50</td>
<td>46.00</td>
<td>115.00</td>
<td></td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hb-SS subjects</td>
<td>76</td>
<td>164.30</td>
<td>8.20</td>
<td>135.00</td>
<td>182.50</td>
<td>0.077</td>
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<tr>
<td>Controls</td>
<td>76</td>
<td>166.10</td>
<td>8.24</td>
<td>150.00</td>
<td>190.00</td>
<td></td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb-SS subjects</td>
<td>76</td>
<td>21.80</td>
<td>4.20</td>
<td>15.80</td>
<td>40.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Controls</td>
<td>76</td>
<td>25.05</td>
<td>4.77</td>
<td>17.00</td>
<td>39.00</td>
<td></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb-SS subjects</td>
<td>76</td>
<td>33.75</td>
<td>11.11</td>
<td>18.00</td>
<td>63.00</td>
<td>0.970</td>
</tr>
<tr>
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<td>33.81</td>
<td>9.81</td>
<td>18.00</td>
<td>61.00</td>
<td></td>
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<tr>
<td><strong>FVC % Predicted</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study subjects</td>
<td>71</td>
<td>72.63</td>
<td>22.19</td>
<td>40.00</td>
<td>120.00</td>
<td>0.001</td>
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<tr>
<td>Controls</td>
<td>74</td>
<td>90.38</td>
<td>11.85</td>
<td>53.00</td>
<td>114.00</td>
<td></td>
</tr>
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<td><strong>FEV1 % Predicted</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study subjects</td>
<td>71</td>
<td>65.32</td>
<td>20.55</td>
<td>24.00</td>
<td>115.00</td>
<td>0.001</td>
</tr>
<tr>
<td>Controls</td>
<td>74</td>
<td>87.03</td>
<td>12.84</td>
<td>50.00</td>
<td>115.00</td>
<td></td>
</tr>
<tr>
<td><strong>% Ratio (FEV1/FVC)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study subjects</td>
<td>71</td>
<td>75.64</td>
<td>9.59</td>
<td>50.20</td>
<td>92.20</td>
<td>0.001</td>
</tr>
<tr>
<td>Controls</td>
<td>74</td>
<td>82.16</td>
<td>6.28</td>
<td>67.50</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Relationship between FEV1, FVC percentage predicted values, and anthropometric variables of participants using Spearman's rank correlation analysis.

<table>
<thead>
<tr>
<th></th>
<th>Height (n=144)</th>
<th>Weight (n=142)</th>
<th>BMI (n=139)</th>
<th>Age (145)</th>
</tr>
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<tbody>
<tr>
<td><strong>FEV1 % Predicted</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spearman's rank</td>
<td>0.089</td>
<td>0.271</td>
<td>0.243</td>
<td>0.071</td>
</tr>
<tr>
<td>Correlation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>0.287</td>
<td><strong>0.001</strong></td>
<td><strong>0.004</strong></td>
<td>0.397</td>
</tr>
<tr>
<td><strong>FVC % Predicted</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spearman's rank</td>
<td>0.041</td>
<td>0.187</td>
<td>0.177</td>
<td>0.108</td>
</tr>
<tr>
<td>Correlation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>70.627</td>
<td><strong>0.026</strong></td>
<td><strong>0.037</strong></td>
<td>0.197</td>
</tr>
</tbody>
</table>

compared to 90.4±11.9% and 87±12.8% among the controls (p < 0.001). Analysis showed that 53 (74.6%) and 43 (60.6%) of the Hb-SS participants had abnormal FEV1% and FVC% predicted, respectively (<80%).

Table 2 showed that FEV1 and FVC% predicted values positively correlated with the age, height, weight, and BMI of the participants but these were not statistically significant except for weight and BMI (p<0.05). Gender was also significantly associated with participants FEV1% predicted (p=0.010).

Logistic regression analysis however showed that age, height, gender, weight, and BMI did not significantly influence the presence or absence of abnormal FEV1 and FVC% predicted (Table 3). Also, the odds of having abnormal FEV% and FVC% predicted among the cases were 11.7 and 13.2, respectively (Table 3).

As shown in Table 4, 50(70.4%) of Hb-SS patients compared to 9(12.2%) of the controls had abnormal spirometry outcome (defined as restrictive, obstructive, or mixed restrictive and obstructive defects; p < 0.001). The proportions of abnormal spirometry outcomes among the Hb-SS participants were restrictive (70%), obstructive (16%), and mixed defects (14%), while the controls had restrictive defects only. The mean oxygen saturation was 94.0±1.9% on room air compared to 97±1.6% among the controls (p < 0.001). There was no significant difference between the mean oxygen saturation of Hb-SS participants with normal or abnormal spirometry outcome.

3.3. Association between Laboratory Parameters and Spirometry Outcome of Hb-SS Participants. The mean steady-state haemoglobin of the Hb-SS participants was 8.1 ± 1.6 g/dl with a range of 4.90 – 11.2 g/dl. The mean total WBC was elevated (10.1 ± 3.6 x 10⁹/l) with a range of 3.4–26 x10⁹/l. The mean platelet count was normal 341.4 ± 109.2 x10⁹/l showing a wide range of 143–873 x10⁹/l. Mean blood urea was normal, 3.5 ± 1.6 mmols/l with a mean creatinine of 55.6 ± 20.0 mmols/l. Mean
free plasma haemoglobin was elevated, 105.7 ± 53.4 µg/ml with 66 (91.7%) of the patients having values > 40 µg/ml, indicative of intravascular haemolysis.

From analysis, abnormal spirometry outcome was significantly associated with blood urea level (p=0.033) but not with serum creatinine (p=0.056). A positive correlation was observed between FEV1% predicted and haemoglobin level; R=0.239; p= 0.043 (Table 5). We also found that free plasma Hb were significantly associated with FEV1% predicted. Comparing laboratory factors including Hb, urea, and creatinine with obstructive defects; p=0.034 (Table 6). Further post hoc analysis for pairwise comparison using Dunnett’s test showed that only obstructive and restrictive defects were nearly significantly different (p=0.05), suggesting a lower platelet count among patients with obstructive defects.

Also, TRV, a noninvasive marker of elevated pulmonary artery systolic pressure showed a tendency to be comparatively elevated in those with mixed restrictive and obstructive defect (p=0.056). However, there was no significant association between TRV and percentage predicted values of FEV1 and FVC (Table 7).

3.4. Spirometry Measurements and Associated Clinical Factors.
Hb-SS participants with ≥ 3 sickle cell crisis in the past year had a lower mean FVC% predicted (65.9%) compared to a mean of 75.0% in those with ≤ 2 crisis in the past year (p=0.180). There were no significant differences between participants with or without history of chronic leg ulcer with regard to their FVC and FEV1% predicted values.

4. Discussion
4.1. Participants’ Demographic Characteristics. Generally, children as well as adults with sickle cell disease are believed to be of a lower average body weight and height than their unaffected peers [18–20]. A study by Oguntaye et al. in Nigeria reported that, until the age of 18, the trend in height and weight of children with sickle cell disease is identical to that of their unaffected peers but began to show significant differences after 18 years [21]. They also showed that the gap in anthropometric measurements between the two groups further widened with increasing age. On the other hand, some studies have found no significant height variation among SCD patients 18 years and above when compared to healthy controls, in fact reporting average or above average heights [22, 23]. The current study similarly showed that the Hb-SS subjects were comparable in height to the controls but had significantly lower body weight and BMI. The negative effect of sickle cell disease on growth and development, especially during the adolescence period, has been blamed for this variance; however, the role of nutrition cannot be overlooked [24]. Incidentally the average BMI of our Hb-SS participants (21.80) was comparable to that of the Hb-SS participants (21.30) was comparable to that of the Hb-SS subjectss in a US study by Klings et al. [9]. This could imply comparable nutritional status of the Ghanaian Hb-SS patients to that of the American cohort but improved holistic medical care of sickle cell patients in our part of the world, especially during early childhood, could also influence this pattern.

4.2. Spirometry Parameters and Anthropometry of Participants. The current study showed that measured lung volumes (FEV1 and FVC% predicted) were significantly lower in Hb-SS patients compared to the non-SCD controls and this is consistent with findings from previous studies [6, 22, 25]. Age, gender, standing height, and weight are important determinants of lung function due to their significant correlation with Pulmonary Function Tests and this correlation has similarly been shown in our study [26]. With the established disparity in anthropometric parameters particularly weight, BMI, and sometimes height, it is believed that the observed
Table 5: Correlation between FEV1, FVC percentage predicted, and laboratory parameters using Spearman’s ranked correlation coefficient Rho.

<table>
<thead>
<tr>
<th>Laboratory indices</th>
<th>FEV1% Spearman’s Coefficient Rho</th>
<th>P-value</th>
<th>FVC% Spearman’s Coefficient Rho</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>0.244</td>
<td>0.043</td>
<td>0.200</td>
<td>0.100</td>
</tr>
<tr>
<td>Total WBC</td>
<td>0.081</td>
<td>0.514</td>
<td>0.058</td>
<td>0.637</td>
</tr>
<tr>
<td>Platelet</td>
<td>0.155</td>
<td>0.208</td>
<td>0.010</td>
<td>0.938</td>
</tr>
<tr>
<td>Plasma Hb</td>
<td>-0.108</td>
<td>0.387</td>
<td>-0.115</td>
<td>0.359</td>
</tr>
<tr>
<td>Urea</td>
<td>-0.067</td>
<td>0.568</td>
<td>-0.113</td>
<td>0.393</td>
</tr>
<tr>
<td>Creatinine</td>
<td>-0.039</td>
<td>0.774</td>
<td>0.032</td>
<td>0.810</td>
</tr>
</tbody>
</table>

Table 6: Comparisons of means of laboratory results and TRV with spirometry outcomes among Hb-SS subjects.

<table>
<thead>
<tr>
<th>Spirometry Interpretation</th>
<th>Obstructive</th>
<th>Restrictive</th>
<th>Mixed</th>
<th>Normal</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin Level (g/dl)</td>
<td>8.4±1.8</td>
<td>7.9±1.6</td>
<td>7.3±2.0</td>
<td>8.4±1.3</td>
<td>0.350</td>
</tr>
<tr>
<td>Total Neutrophil count (x10^9/l)</td>
<td>8.5±3.2</td>
<td>10.6±4.0</td>
<td>8.3±1.2</td>
<td>10.3±3.3</td>
<td>0.413</td>
</tr>
<tr>
<td>Platelet Count (x10^9/l)</td>
<td>251.1±58.9</td>
<td>366.6±103.1</td>
<td>308.4±87.8</td>
<td>350.6±127±3</td>
<td>0.034</td>
</tr>
<tr>
<td>Plasma Haemoglobin (ug/ml)</td>
<td>94.8±46.8</td>
<td>132.4±81.3</td>
<td>99.7±34.5</td>
<td>115.9±83.3</td>
<td>0.699</td>
</tr>
<tr>
<td>Creatinine</td>
<td>6.4±17.3</td>
<td>57.8±22.8</td>
<td>61.7±28.0</td>
<td>49.4±10.8</td>
<td>0.372</td>
</tr>
<tr>
<td>Urea</td>
<td>3.1±0.5</td>
<td>3.9±2.0</td>
<td>4.1±2.1</td>
<td>2.9±0.6</td>
<td>0.203</td>
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<tr>
<td>FVC%</td>
<td>87.6±15.6</td>
<td>61.4±11.4</td>
<td>57.3±11.6</td>
<td>94.1±16.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV1%</td>
<td>61.8±21.3</td>
<td>56.9±11.2</td>
<td>43.0±9.6</td>
<td>88.1±18.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Freq of crisis/year</td>
<td>0.5±0.8</td>
<td>1.5±1.3</td>
<td>1.1±0.9</td>
<td>1.1±1.4</td>
<td>0.410</td>
</tr>
<tr>
<td>TRV (m/s)</td>
<td>2.4±0.3</td>
<td>2.3±0.4</td>
<td>2.6±0.4</td>
<td>2.2±0.4</td>
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</table>

Table 7: Association between FEV1, FVC percentage predicted, and TRV values.

<table>
<thead>
<tr>
<th>FEV1 % Predicted</th>
<th>TRV</th>
<th>Normal n(%)</th>
<th>Elevated n(%)</th>
<th>X^2-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 80%</td>
<td></td>
<td>36 (67.9)</td>
<td>17 (32.1)</td>
<td>0.570</td>
</tr>
<tr>
<td>&gt; 80%</td>
<td></td>
<td>12 (66.7)</td>
<td>6 (33.3)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>FVC % Predicted</th>
<th>TRV</th>
<th>Normal n(%)</th>
<th>Elevated n(%)</th>
<th>X^2-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 80%</td>
<td></td>
<td>29 (65.9)</td>
<td>15 (34.1)</td>
<td>0.452</td>
</tr>
<tr>
<td>&gt; 80%</td>
<td></td>
<td>19 (70.4)</td>
<td>8 (29.6)</td>
<td></td>
</tr>
</tbody>
</table>

The presence of the disease predisposes to abnormal lung function. These suggest that reduced lung volumes in Hb-SS patients comparative to non-SCD controls may result from a combination of factors/complications of the disease and not merely due to anthropometric variance although the latter may be contributing to it. It can be inferred from this analysis that the mere presence of Hb-SS is a significant predictor of abnormal lung function. Some studies have reported diminished respiratory muscle strength in children and young adults with SCD which could also partly explain the lower lung volumes [28, 29].

4.3. Prevalence of Abnormal Spirometry among Hb-SS Patients and Associated Factors. The study found that a significant proportion (70.4%) of the Hb-SS participants had abnormal spirometry outcome, with restrictive defect being predominant. In a US study by Klings et al., as much as 90% of the Hb-SS participants had abnormal lung function including 13% with impaired DLco [9]. Our proportion was comparatively lower and this could be due to our inability to test for diffusion capacity (DLco). Similar to our study, Dosunmu and colleagues in Nigeria found that 68% of the SCD participants had abnormal spirometry outcome, of which 53% had restrictive defects, 3.7% obstructive defects and 11% with mixed defects [8]. These consistent results more prove the predominance of restrictive defects among adults with sickle cell disease [6–9, 30, 31]. Abnormal lung function, particularly, restrictive defects in Hb-SS, has been shown to be more prevalent in those with a severe disease.
an association between steady-state Hb and FVC% predicted; FEV1% predicted but Williams and colleagues rather found steady-state haemoglobin showed a positive correlation with haemolysis among SCD patients [41]. We also found that an association between FEV1% predicted and markers of was consistent with findings by Sylvester et al. who found in SCD, likely through sickle cell associated vasculopathy [9].

A prospective study by Aquino and colleagues reported a significant correlation between the severity and extent of parenchymal abnormalities on chest CT-scan and the number of prior ACS [33]. Maioli and colleagues in Brazil also found an association between a history of ACS and restrictive defects on spirometry [34]. In our study, we were unable to obtain a definite history of ACS due to diagnostic challenges that existed but observed that patients with increased frequency of crisis (3 or more in the past year), largely VOC in nature, had lower FVC % predicted values when compared to those with 2 or less episodes of sickle cell crisis in a year (65.9% predicted versus 75.0% predicted, respectively; p=0.180). This supports the notion that recurrent VOC crisis could cause ischaemic damage to the lung parenchyma with fibrosis via the release of inflammatory mediators from the damaged endothelium and hypoxic lung and hence the decrease in lung volumes [35, 36]. Obstructive defects, however, have been reported to be more prevalent among children with SCD in whom asthma-like symptoms and airway hyperreactivity could occur [37, 38]. The study by Klings et al. [9] and Dosunmu et al. [8] found low prevalence of obstructive defects in the adult SCD population studied. In contrast, Vendramini and colleagues [25] however reported a high prevalence (31%) of obstruction and airway hyperreactivity among adults with SCD. Our proportion of adult SCA patients with obstructive defects was 16% which was similar to 19.5% observed by Williams et al. [6]. The causes of obstruction in SCD are more complex and quite unclear but thought to include inflammation, effects of hypoxia, and oxidative stress on the bronchial tree [25].

Sickle cell vasculopathy is a complication in SCD attributed to the toxic effects of products of intravascular haemolysis and has been linked to the development of pulmonary hypertension, chronic leg ulcers, chronic kidney disease, and chronic lung complications in sickle cell patients [39, 40]. Similar to the above observation, our analysis showed that free plasma Hb levels above 40ug/ml, evident of intravascular haemolysis, were significantly associated with abnormal FEV1% predicted (< 80% predicted) and this was consistent with findings by Sylvester et al. who found an association between FEV1% predicted and markers of haemolysis among SCD patients [41]. We also found that steady-state haemoglobin showed a positive correlation with FEV1% predicted but Williams and colleagues rather found an association between steady-state Hb and FVC % predicted; p < 0.001 [6, 42]. However on linear multivariate analysis, Hb or free plasma haemoglobin significantly predicted abnormal FEV1%.

Our study also showed a significant association between abnormal spirometry outcome and blood urea level (p = 0.033) with a rising trend of creatinine level in those with abnormal spirometry (p = 0.056). These observations support suggestions from previous studies of a possible common aetiological link between chronic lung disease and kidney disease in SCD, likely through sickle cell associated vasculopathy [9].

It has been proposed that activated white blood cells and platelets promote vascular inflammation and vessel damage. They are therefore likely to play a role in initiating sickle cell vasculopathy and hence the development of perivascular lung parenchymal fibrosis with effects on measured lung volumes [35]. Dosunmu and colleagues reported a negative correlation between total WBC and platelet counts with the FVC% predicted among the studied SCD cohort [8]. We observed that the mean platelet count had a tendency to be lower among those with obstructive defects (p =0.05). Studies by Gladwin et al. and Anthi et al. have shown that SCD patients with raised pulmonary artery systolic pressure usually show a restrictive pattern on spirometry [16, 43]. We have shown that TRV had a tendency to be higher in Hb-SS patients with spirometry defects, particularly in those with mixed defects (TRV of 2.6 ± 0.4; p = 0.056).

In conclusion, the current study has shown that lung volumes are significantly lower in Hb-SS patients when compared to non-SCD controls. The mere presence of the disease strongly predicts abnormal lung function. With the high prevalence of lung function abnormalities among Hb-SS patients, one may suggest that the former could itself be considered a marker of disease severity and hence periodic screening with spirometry may be necessary to allow for patient categorization and further management.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declared no conflicts of interest.

Authors’ Contributions

Yvonne Dei-Adomakoh and Jane Afriyie-Mensah designed the research, data interpretation, and manuscript writing. Martin Adadey, Audrey Forson, and Joseph Acquaye helped in the interpretation of data and made a major contribution in the writing of the manuscript. Thomas Ndanu contributed to data interpretation, statistical analysis, and manuscript writing. All authors read and approved the final version of the manuscript.

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