Introduction

Sickle cell disease (SCD) affects 1 in every 365 Black/African American children in the United States [1]. Vaso-occlusive pain crises (VOC) are the most common complication of SCD [2]. Frequent VOC is associated with increased morbidity, mortality, and increased healthcare utilization [3,4]. While the majority of VOC are managed at home, some patients present to the emergency department (ED) for pain management [5,6]. Of the SCD subtypes (HbSS, SC, SB<sup>0</sup> thalassemia and SB<sup>+</sup>), HbSS is the most common sickle cell subtype. Traditionally, HbSS has been associated with more severe disease and more frequent pain crises [4]. Despite well-identified disease processes, ED utilization for VOC is highly variable and poorly explained by SCD's single genetic variant.

The objective of this study was to identify demographic and disease-related predictors of ED utilization and hospitalization for VOC in pediatric patients with SCD [7]. We hypothesized that HbSS genotype, male, public insurance, visit during winter months, and worse blood laboratory values would be associated with high ED utilization [8,9] and predict total number of ED SCD visits and hospitalizations. We further examined whether ED length of stay, time till roomed, time till opioid analgesia, and total opioid dosage impacted healthcare utilization [10-12].
Research Methodology

Study design

Institutional IRB approval was obtained for an electronic health record-review from July 1, 2012 to October 25, 2018. Inclusion criteria: (1) SCD HbSS, SC, SBβ thalassemia, or SBβ thalassemia, (2) 5-19 years, and (3) admitted to pediatric ED for VOC only (ICD 9 and ICD 10 codes). An ED visit was included if the disposition was “discharge to home”, “inpatient admission” or “inpatient observation”. Patients who left against medical advice, eloped, or had non-VOC diagnosis were excluded (e.g., fever, acute chest syndrome, bone marrow failure).

Clinical investigation

Primary outcomes: ED visit was defined as registered in the pediatric ED. Hospitalized was defined as ED disposition of “inpatient admission” or “inpatient observation”. Total number of ED visits and total number of hospitalizations were summed across the six year study period. Patients had High ED Utilization if they had ≥3 ED visits during any year.

Demographic and disease predictors: Demographics included age at visit, sex, race, SCD genotype, time of year (Winter, Spring, Summer, Fall) [13], and insurance. Body mass index [14], hemoglobin (Hgb), hematocrit (Hct), reticulocyte count (retic), mean corpuscle volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and mean corpuscular hemoglobin (MCH) were extracted for each visit [15-17]. Severe SCD disease severity criteria: (1) SCD HbSS, SC, SB+ thalassemia, or SB + thalassemia, 0 thalassemia, or SBβ thalassemia, and insurance (0=Federal/self-pay; 1=private) were included as between-person predictors.

Descriptive statistics for 248 patients across 1,363 ED visits are in Table 1. Patients were predominantly African American (99.6%).

Exploratory variables

We examined whether ED length of stay (minutes), ED time until roomed (minutes), time till initial opioid administration, and total opioid dose (morphine equivalents/kilogram) were predictive of hospitalization for VOC [20,21].

Statistical analysis

Descriptive statistics, non-parametric one sample tests (males vs females; time of year), t-tests for continuous and chi-squared for categorical group differences were calculated in IBM SPSS 26 (IBM Corp). Linear and logistic regression models included mean values for predictors that varied across visits. Multilevel models for binary outcomes were specified using hierarchical linear models (HLM v.8) [22] to account for nesting of hospital visits within patients. ‘Visit number’ was included in all models, along with predictors that varied across visits: age, BMI, Hgb, Retic, MCV result, MCHC level, ED length of stay, ED time until roomed, time till initial opioid, and total opioid dose. Hct and MCH were highly correlated with other laboratory values (r’s > .7) and were removed from regression and multilevel models. Genotype (1=SS/βthalassemia; 2=SC/βthalassemia), sex, and insurance (0=Federal/self-pay; 1=private) were included as between-person predictors.

Results

Participant characteristics

Descriptive statistics for 248 patients across 1,363 ED visits are in Table 1. Patients were predominantly African American (99.6%).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Low ED Utilization N=93</th>
<th>High ED Utilization N=158</th>
<th>Test statistic (p-value)</th>
<th>Total Sample n (%)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>44 (%4.03)</td>
<td>88 (3.76)</td>
<td>-4.91 (&lt;0.001)</td>
<td>132 (52.6)</td>
<td>5-19</td>
</tr>
<tr>
<td>Female</td>
<td>49 (5.41)</td>
<td>70 (5.76)</td>
<td>-3.09 (&lt;0.01)</td>
<td>119 (47.4)</td>
<td>11-99</td>
</tr>
<tr>
<td>Hb, SS/βthalassemia</td>
<td>62 (1.75)</td>
<td>107 (4.64)</td>
<td>-1.75 (0.08)</td>
<td>9.16 (1.67)</td>
<td>4.1-16.8</td>
</tr>
<tr>
<td>Hb, SC/βthalassemia</td>
<td>31 (2.46)</td>
<td>51 (4.64)</td>
<td>-1.32 (0.19)</td>
<td>26.03 (4.74)</td>
<td>13.1-45.1</td>
</tr>
<tr>
<td>Private/Military insurance*</td>
<td>9 (8.89)</td>
<td>20 (4.71)</td>
<td>0.44 (0.66)</td>
<td>7.89 (4.41)</td>
<td>0.1-18.1</td>
</tr>
<tr>
<td>Public/No insurance*</td>
<td>84 (79.56)</td>
<td>138 (84)</td>
<td>0.51 (0.48)</td>
<td>222 (88.4)</td>
<td>29.3-39.7</td>
</tr>
<tr>
<td>M (SD)</td>
<td>11.84 (3.76)</td>
<td>83.08 (10.50)</td>
<td>-3.31 (&lt;0.01)</td>
<td>82.78 (10.55)</td>
<td>54.0-121.8</td>
</tr>
<tr>
<td>MCHC level</td>
<td>8.09 (4.71)</td>
<td>7.87 (4.38)</td>
<td>0.44 (0.66)</td>
<td>7.89 (4.41)</td>
<td>0.1-18.1</td>
</tr>
<tr>
<td>MCV</td>
<td>34.87 (15.7)</td>
<td>35.26 (16.2)</td>
<td>-2.39 (0.02)</td>
<td>35.23 (16.2)</td>
<td>29.3-39.7</td>
</tr>
<tr>
<td>M (SD)</td>
<td>35.26 (16.2)</td>
<td>35.23 (16.2)</td>
<td>-2.39 (0.02)</td>
<td>35.23 (16.2)</td>
<td>29.3-39.7</td>
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<tr>
<td>MCH</td>
<td>121.8</td>
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<td>-6.56 (&lt;0.001)</td>
<td>9.48 (12.21)</td>
<td>1-94</td>
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<td>M (SD)</td>
<td>121.8</td>
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<td>-6.56 (&lt;0.001)</td>
<td>9.48 (12.21)</td>
<td>1-94</td>
</tr>
</tbody>
</table>

Notes: *insurance payer was collected for first ED visit for each patient.
*Total ED and total hospitalizations per patient are summed over the six year study period.
Mean age at first ED visit was 9.7 (SD=3.9). Thirty patients (12.1%) had one ED visit, 100 patients (40.3%) had two to five visits, and 118 patients (47.6%) had six or more visits. All patients had normal BMI, except for one visit reflecting obesity. ED visits were evenly distributed across time of year (Chi-Squared=1.23, p=0.75). A subset of 61 patients (24.6%) were classified as having High ED Utilization.

### High versus low ED utilization

A substantial subset (62.9%) of patients classified as having High ED Utilization. Patients with High ED Utilization were typically older, had severe SCD disease, had lower Hgb levels, had lower MCV, and had more hospitalizations than Low ED Utilization counterparts (p's <0.05; Table 1).

### Predicting total number of ED visits and hospitalizations

SCD genotype, demographic (age at visit, sex), BMI, and laboratory values (Hgb, retic, MCV, MCHC) at ED admission were not significantly associated with total number of ED visits or total number of hospitalizations in linear regression models (all p's >0.05).

### Predicting High ED Utilization

A logistic regression model revealed that age, BMI, and laboratory value were not significantly associated with High ED utilization (all p's >0.05).

### Predicting hospitalization

The odds of being hospitalized decreased as patients’ number of visits increased (Table 2). Higher BMI and lower Hgb level were associated with increased likelihood of hospitalization. No laboratory values were associated with hospitalization. Specific to the ED visit, longer ED visits were associated with decreased odds of hospitalization. However, longer time until receiving first opioid and higher total morphine equivalency dosage was associated with increased likelihood of hospitalization for VOC.

### Discussion

Compared to their Low ED Utilization counterparts, patients with High ED Utilization (62.9%) tended to be older, have severe SCD disease, have lower Hgb levels, and have lower MCV result. Early identification and recognition of these higher risk patients in the outpatient setting may allow for earlier healthcare intervention and decreased hospital utilization [23,24]. Despite examining a range of demographic and medical laboratory predictors we did not identify any significant predictors of total ED visits, total hospitalizations, or High ED Utilization in regression analyses. These null findings are consistent with previous literature and suggest that the frequency of SCD VOC complications is highly individual.

Lower Hgb level, requiring more opioid medications, and requiring a longer ED length of stay are reflective of the clinical picture leading to hospitalization. At our institution, time to initial opioid administration fell in line with the current National Lung Blood and Heart Institute (NHLBI) recommendations for opioid administration within 1 hour. However, initial opioid morphine equivalency dosage was frequently low for weight status, and may have been inadequate to treat VOC, contributing to a higher hospitalization rate.

### Limitations

In this clinical setting, there is risk that patient diagnoses were misclassified, coding differences occurred between ICD 9 and ICD 10 codes, and changes in practice occurred after 2014 NHLBI recommendations published during this study period. While our institution is the only pediatric hospital in the state, it is likely not all VOC ED visits were captured due to patients being seen at their local ED and 16 years and older occasionally alternating care between the pediatric and adult ED.

### Conclusion

Based on the current study and larger literature, the strongest predictors of high ED utilization in pediatric patients with SCD include older age, HbSS subtype, lower Hgb level, and prior history of complication (i.e., severe SCD disease). Additional studies are critically needed to identify novel predictors of high ED utilization and test standardized interventions in both the outpatient and ED setting.
Conflict of Interest

Authors declare no conflict of interest.

Acknowledgements

There was no funding for this study.

References