Distance from an Urban Sickle Cell Center and its Effects on Routine Healthcare Management and Rates of Hospitalization

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Abstract

The St. Jude Children’s Research Hospital (St. Jude) comprehensive sickle cell center serves a 150 mile catchment radius around Memphis, TN, USA. Full travel expenses are provided for routine and acute care visits for sickle cell disease patients living ≥35 miles from St. Jude. We compared hospitalization rates to national estimates and assessed if driving distance was a barrier to sickle cell healthcare despite the travel reimbursement policy. We evaluated the associations between hospitalizations and routine clinic visits and distance from St. Jude using negative binomial models and we conducted bias analyses by Monte Carlo simulation. We followed 545 patients (2550 patient-years) aged ≤18 years with sickle cell disease (Hb SS only) from 2007 to 2012. The hospitalization rate per patient-year was 0.65 (95% CI (confidence interval): 0.62, 0.68), significantly lower than the national rate of 1.16 (95% CI: 1.14, 1.18). Children living <35 miles from St. Jude had 1.75 (95% CI: 1.41, 2.17) times the rate of hospitalization and 1.22 (95% CI: 1.07, 1.39) times the rate of clinic visits compared to those ≥35 miles. Bias analysis suggested that under-reporting could explain the observed difference in hospitalization rates if 30.0% of patients who lived ≥35 miles from the hospital under-reported six hospitalizations over 6 years. The hospitalization rate at St. Jude in children with sickle cell disease was lower than expected from national rates. Greater distance from the sickle cell center (>35 miles) was associated with decreased hospitalization rates, despite the travel allowances that are provided for those who live ≥35 miles from the hospital.

Introduction

Sickle cell disease is an inherited hematological disorder that affects the hemoglobin (Hb) content of red blood cells (RBCs) (1). Complications occur throughout the life-time of the patient, and include severe pain crises, chronic organ damage, and a shortened life (1). In the United States sickle cell disease occurs primarily in African Americans, occurring in approximately one in 350 live births (2,3).

Due to the chronic nature of sickle cell disease, adequate treatment requires consistent, multi-disciplinary care. Preventive care starts from infancy with penicillin prophylaxis, immunizations, and disease education, all requiring frequent clinical encounters (1). Common treatments such as hydroxyurea (HU) therapy or chronic transfusions also require frequent visits to monitor efficacy and toxicities (4). Complications such as vaso-occlusive crises (VOCs) and acute chest syndrome (ACS), can occur frequently and unpredictably in persons with sickle cell disease; therefore, unplanned hospitalizations are often necessary for acute management of these serious conditions (5).

Hospital utilization for those with sickle cell disease in the United States has been quantified on a national level by Broussseau et al. (6). Persons with the more severe sickle cell disease genotypes, Hb SS (β⁰/β⁰) and Hb S-β⁰-thalassemia (Hb S-β⁰-thal), typically require more frequent hospitalizations than those with less severe genotypes (1). Progressing from childhood to adolescence to young adulthood has been associated with increased rates of acute care and decreased adherence with health maintenance visits, especially among sickle cell disease patients without private health insurance (7,8).

Both distance to a hospital and low socioeconomic status have been shown to affect healthcare access for some populations (9,10). Although results are not definitive, persons living in rural areas appear to have greater barriers to care than those in urban areas (11,12). However, socioeconomics can be a factor when evaluating the differences between rural and urban health care access, and persons in higher income groups may be better able to overcome these barriers (9,10,13). For example, a recent study found higher rates of successful...
transition to adult sickle cell disease care for persons living within 20 miles of a sickle cell disease center (14).

At St. Jude Children’s Research Hospital (St. Jude), care is provided at no charge to the patient, regardless of insurance status. To help combat distance as a barrier to health care access, mileage reimbursement and travel planning services are provided for patients living 35 miles or greater from the St. Jude campus. When necessary, St. Jude provides housing for out of town patients and families free of charge. Despite the availability of assistance with travel aimed at facilitating optimal healthcare availability, we had not formally investigated whether this service is an effective means of optimizing adherence with medical visits or if distance is still a barrier to receiving consistent treatment for sickle cell disease at St. Jude.

Accordingly, we first sought to determine if hospitalization rates of patients followed in the St. Jude sickle cell center were similar to national published rates (6). Second, we aimed to evaluate the association between travel distance from the sickle cell program and the frequency of clinic visits and hospitalizations. Despite the travel assistance provided for those more than 35 miles from St. Jude, we hypothesized that persons living 35 miles or farther from campus had fewer clinic visits and hospitalizations than those living within 35 miles. Our ultimate goal was to improve patient care and inform public health endeavors by better understanding the effects of distance and other barriers to healthcare access and management.

Methods

The pediatric sickle cell disease program at St. Jude, located in Memphis, TN, USA, serves a catchment area with a 150-mile radius, encompassing portions of Tennessee, Arkansas, and Mississippi. The hospital is located in a major urban area, serving both rural and urban populations. Only patients with Hb SS ($\beta^S/\beta^S$) disease currently followed by St. Jude, who live within 150 miles of the center and were seen at least once during the 6-year period (2007 to 2012), were included in these analyses.

Patients were classified into groups based on the number of driving miles from their primary residence to St. Jude, estimated using “mapquest” (http://www.mapquest.com). Because full reimbursement of travel costs is provided for patients living $\geq 35$ miles from St. Jude, patients were dichotomized at 35 miles ($< 35 \text{ vs. } \geq 35$ miles). We also evaluated distance as a four-category variable ($< 35$ miles, $\geq 35$ miles to $< 70$ miles, $\geq 70$ miles to $< 105$ miles, $\geq 105$ miles to $\leq 150$ miles).

All routine clinic visits and hospitalization records from St. Jude from 2007 to 2012 were reviewed. Routine clinic visits are scheduled for sickle cell disease patients at least one time every 6 months and as often as once per month. The majority of in-patient hospitalizations occur at St. Jude or Le Bonheur Children’s Medical Center (LBCMC) in Memphis, TN, USA, (located 1 mile away from St. Jude. Records for both hospitals are electronically captured and maintained by the St. Jude sickle cell disease program in a clinical database. Hospitalizations at other institutions are reported to St. Jude by the provider or patient self-report and corroborating records are sought and obtained when possible. At every routine clinic visit, patients are asked to report all hospitalizations since their last visit.

Information collected for the patients included race, gender, age at study entry, and the percent of study time on HU therapy (for those so treated). Place of residence was classified into four categories (Metropolitan, Micropolitan, Rural, Small Town) using Rural-Urban Commuting Area (RUCA) codes based on the 2006–2010 American Community Survey and 2010 United States Census data (http://www.ers.usda.gov/data-products/rural-urban-commuting-area-codes.aspx). Annual household income ($0-$20,000, $20,000-$40,000, $40,000-$60,000, $\geq 60,000$) was estimated from zip codes using the 2010 American Community Survey (United States Census Bureau). State of residence was evaluated as a categorical variable (Tennessee, Arkansas, Mississippi). This research was approved by the Institutional Review Boards at the University of Memphis and St. Jude.

Statistical analysis

Rates of hospitalizations and clinic visits were summarized by patient-year and compared between St. Jude patients and national rates of hospitalization using the exact Poisson distribution (6). Associations between hospitalizations and routine clinic visit counts and distance from St. Jude were evaluated with negative binomial models and reported as incidence rate ratios (IRRs) (15,16). The potential impact of under-reporting of hospitalizations was evaluated using quantitative bias analysis (17). The Type I error rate for all analyses was set at 0.05 and all analyses were conducted in SAS, version 9.3 (SAS Institute Inc., Cary, NC, USA) or R version 9.13.2 (The R Foundation for Statistical Computing; http://www.r-project.org). Additional details of the statistical analyses are reported in Supplemental Methods.

Results

There were 598 patients (2830 patient-years) with Hb SS followed by St. Jude between 2007 and 2012. The average age at study entry was 6.1 (range: 0 to 18) years. Of the 598 patients, 53 (8.9%) were on chronic transfusion therapy, leaving 545 patients for the primary analysis. Separate analyses of the patients on chronic transfusion therapy are presented in Supplemental Results. Of the 545 patients, 52.8% were male and 65.3% lived within 35 miles of St. Jude. The majority of the patients lived in metropolitan areas (71.6%) and in zip codes with a median household income between $20,000 and $40,000 annually (73.8%) (Table 1). The majority of the patients resided in Tennessee (66.6%), followed by Mississippi (23.7%) and Arkansas (9.7%). Hydroxyurea therapy was initiated in 35.6% of the patients and approximately 25.0% of the total patient-years contributed were after initiation of HU. Three patients died during the study period.

The 545 patients had 1663 hospitalizations over 2550 patient-years of follow-up, yielding a rate of 0.65 (95% CI: 0.62, 0.68) hospitalizations per patient-year. This rate is significantly lower ($p$ value <0.0001) than the national rate of 1.16 (95% CI: 1.14, 1.18) for Hb SS patients aged 1 to 17 as derived from Broussau et al. (6). Patients living within 35 miles of St. Jude had a hospitalization rate of 0.78 (0.74, 0.82)
Table 1. Frequency of the subjects' characteristics by variable groups.

| Parameters                        | n (total = 545) | %    |
|-----------------------------------|-----------------|------|
| Distance from hospital            |                 |      |
| <35 miles                         | 356             | 65.3 |
| ≥35 miles                         | 189             | 34.7 |
| Hydroxyurea therapy               |                 |      |
| no                                | 351             | 64.4 |
| yes                               | 194             | 35.6 |
| Gender                            |                 |      |
| females                           | 257             | 47.2 |
| males                             | 288             | 52.8 |
| State                             |                 |      |
| Arkansas                          | 53              | 9.7  |
| Mississippi                       | 129             | 23.7 |
| Tennessee                         | 363             | 52.8 |
| RUCA classification               |                 |      |
| metropolitan^a                    | 390             | 71.6 |
| micropolitan^b                    | 61              | 11.2 |
| rural                             | 23              | 4.2  |
| small town                        | 69              | 12.7 |
| missing                           | 2               | 0.4  |
| Income group                      |                 |      |
| $0 to $20,000                     | 10              | 1.8  |
| $20,000 to $40,000                | 402             | 73.8 |
| $40,000 to $60,000                | 69              | 12.7 |
| ≥$60,000                          | 54              | 9.9  |
| missing                           | 10              | 1.8  |

RUCA: rural-urban commuting area.  
^aUrban area with at least 50,000 residents.  
^bUrban area with between 10,000 and 50,000 residents.

Table 2. Univariate models for hospitalizations and routine clinic visits by distance from hospital.

| Parameters                        | Hospitalizations IRR (95% CI) | Clinic visits IRR (95% CI) |
|-----------------------------------|-------------------------------|--------------------------|
| Distance from hospital            |                               |                          |
| <35 miles                         | 1.75 (1.41, 2.17)             | 1.22 (1.07, 1.39)        |
| ≥35 miles                         | 1.00 (referent)               | 1.00 (referent)          |
| Distance from hospital            |                               |                          |
| <35 miles                         | 2.31 (1.37, 3.90)             | 1.58 (1.17, 2.12)        |
| ≥35 miles to <70 miles            | 2.22 (1.25, 3.95)             | 1.48 (1.06, 2.06)        |
| ≥70 miles to <105 miles           | 0.76 (0.43, 1.36)             | 1.23 (0.89, 1.70)        |
| ≥105 miles to 150 miles           | 1.00 (referent)               | 1.00 (referent)          |

IRR: incidence ratio; 95% CI: 95% confidence interval.

per patient-year, significantly lower than the national rate of 1.16 per patient-year (p value <0.0001) (6). There were a total of 14,937 routine clinic encounters, with an overall rate of 5.86 (95% CI: 5.76, 5.95) per patient-year.

We found patients living within 35 miles of the hospital had 1.75 (95% CI: 1.41, 2.17) times the rate of hospitalization than those living 35 miles away or greater (Table 2). When distance was evaluated in four groups (<35 miles, ≥35 to <70 miles, ≥70 to <105 miles, ≥105 to ≤150 miles), we found decreasing hospitalization rates as distance from the hospital increased, until reaching 105 miles (Table 2). Patients in the ≥105 to ≤150 miles group had slightly higher rates than those in the ≥70 to <105 miles group, although the 95% CIs indicated that this difference could have been due to random variation.

A similar association was found when evaluating the association of distance and routine clinic visits, although the effect was weaker than the effect of distance on hospitalization. Specifically, we found that persons living within 35 miles of the hospital had 1.22 (1.07, 1.39) times the rate of routine clinic visits compared to those living 35 miles away or greater (Table 2). Similarly to the hospitalization rates, when rates of routine clinic visits were evaluated using the four distance groups, we found decreasing rates of routine clinic visits with increasing distance from the hospital (Table 2). Models individually adjusted for the potential confounders previously described yielded IRRs that were all within 10.0% of the unadjusted IRRs. Therefore, we found no evidence of confounding and present only the unadjusted estimates.

Persons living in metropolitan areas had an increased rate of both hospitalizations [IRR: 1.76 (1.27, 2.44)] and routine clinic visits [IRR: 1.28 (1.06, 1.54)] compared to persons living in a small town. Additionally, persons living in Arkansas [IRR: 0.69 (0.48, 1.00)] and Mississippi [IRR: 0.70 (0.55, 0.90)] had decreased rates of hospitalizations compared to those living in Tennessee. There were no significant differences in routine clinic visits by state. No significant differences were observed in hospitalizations by income group, gender or age. Routine clinic visits increased slightly with increasing age and did not differ by income group or gender. We found increased rates of hospitalizations and routine clinic visits for patients with longer time on HU therapy (Table 3). When comparing hospitalizations specifically for ACS, no significant difference was found between persons living within 35 miles and those living 35 miles away or greater [IRR: 1.23 (0.88, 1.71)].

The potential effect of under-reporting of hospitalizations on our observed association between distance and hospitalizations was evaluated in a bias analysis. We found that differential under-reporting between patients living <35 and ≥35 miles from the hospital could have an impact on the IRR. If no under-reporting occurred for patients living <35 miles from St. Jude and 30.0% of patients living ≥35 miles failed to report three hospitalizations over the 6-year study period, the IRR for distance was estimated as 1.2, compared with the observed IRR of 1.7. Under the same conditions, if 30.0% of patients ≥35 miles under reported by six hospitalizations in the 6-year period, the IRR ratio estimate was further reduced to 0.9. Misclassification of distance group was also evaluated as a potential source of bias in this study (Supplemental Results).

Discussion

Results from this evaluation indicate that Hb SS patients treated at St. Jude were hospitalized approximately half as often as expected based on population-based data in the United States (6). Several factors could contribute to this observed difference. First, under-reporting is possible; however, because 65.3% of our patient population lives within 35 miles of St. Jude, we would expect the majority of hospitalizations to occur at St. Jude where data are electronically collected and not subject to self-reporting. Second, St. Jude has an acute care clinic onsite that is staffed by pediatric hematologists experienced with sickle cell disease to provide optimal care for persons with sickle cell disease in an outpatient setting. Visiting the specialized acute care clinic...
The results of this report suggest that distance from the sickle cell center is associated with the rate of hospitalization. Specifically, we found that patients living within 35 miles of the hospital had a significantly higher rate of hospitalization than those living 35 miles or farther. This result was further supported by the progressive effect of distance on hospitalizations that we observed when distance was classified into smaller categories. We found a similar pattern when the association between routine clinic visits and distance was evaluated.

An association between HU treatment and hospitalization rates has been reported from several studies; therefore, we evaluated if HU use could also be associated with distance and potentially confound our results. We found no evidence of confounding due to HU therapy on the association between distance and hospitalization. However, the duration of HU therapy was associated with an increase in the rate of hospitalizations. Hydroxyurea therapy has historically been recommended for patients based on clinical severity. Therefore, after excluding patients on chronic transfusion, patients who are prescribed HU are likely to have a more severe disease than those who are not prescribed HU. This difference in clinical severity may explain the higher rate of hospitalizations found in this study. In contrast, a recent study from St. Jude that only included subjects on HU therapy found a slight decrease in hospitalizations after initiation of HU (18). This result was consistent with the report of significantly fewer hospitalizations in those randomized to the HU arm of the BABY HUG study (19).

Evaluation of routine clinic visits per patient-year indicates an increased rate while on HU therapy. This result is expected because patients on HU therapy are monitored with greater frequency for possible toxicities of therapy, and are therefore required to come to the sickle cell clinic more often. More than 85.0% of these patients were being treated on a clinical study related to HU, indicating that measures were taken to encourage adherence.

The observed difference in hospitalization rates between patients <35 or ≥35 miles from St. Jude could conceivably be affected by under-reporting of hospitalizations. Patients living farther from the sickle cell center may be more likely to seek treatment at a local hospital other than the sickle cell center. Because these hospitalizations are not recorded automatically in the St. Jude clinical database, under-reporting of hospitalizations among patients ≥35 miles from St. Jude may occur. We found that under-reporting could explain all of the observed difference in hospitalization rates if 30.0% of the patients living ≥35 miles away under-reported six hospitalizations each over the course of the 6-year study. Unfortunately, we have no data to assess whether this large degree of differential under-reporting is plausible.

Frequency of hospitalization is a determinant of clinical severity and has been used to establish eligibility for HU therapy (20). Even if all observed differences in hospitalization rates are due to under-reporting, the severity of disease in persons living farther from the sickle cell center could be underestimated leading to less treatment with HU. It is also possible that the difference in hospitalizations exists because patients with more severe disease tend to live closer to sickle cell centers.

All routine visits to the sickle cell clinic are recorded electronically in the clinic database. Therefore, under-reporting is not a concern for the routine clinic visits in this study. The higher rate of clinic visits among those <35 miles suggest that the current efforts to increase healthcare accessibility are not sufficient to eliminate the effect of distance. Travel time and transportation issues are likely deterrents that are potentially contributing to the differences. Hospital assistance efforts may be able to temper this, but short of relocation, distance is not a modifiable factor.

| Parameter                  | Hospitalizations IRR (95% CI) | Clinic visits IRR (95% CI) |
|----------------------------|-------------------------------|---------------------------|
| Gender                     |                               |                           |
| females                    | 1.01 (0.82,1.25)              | 1.04 (0.92, 1.17)         |
| males                      | 1.00 (referent)               | 1.00 (referent)           |
| State                      |                               |                           |
| Arkansas                   | 0.69 (0.48, 1.00)             | 0.89 (0.72, 1.10)         |
| Mississippi                | 0.70 (0.55, 0.90)             | 0.89 (0.77, 1.03)         |
| Tennessee                  | 1.00 (referent)               | 1.00 (referent)           |
| RUCA classification        |                               |                           |
| metropolitan*              | 1.76 (1.27, 2.44)             | 1.28 (1.06, 1.54)         |
| micropolitan*              | 0.95 (0.61, 1.48)             | 0.99 (0.77, 1.27)         |
| rural                      | 2.07 (1.16, 3.67)             | 1.32 (0.93, 1.86)         |
| small town                 | 1.00 (referent)               | 1.00 (referent)           |
| Income group               |                               |                           |
| $0 to $20,000              | 1.48 (0.68, 3.22)             | 0.93 (0.57, 1.50)         |
| $20,000 to $40,000         | 0.94 (0.66, 1.33)             | 0.80 (0.65, 0.99)         |
| $40,000 to $60,000         | 0.88 (0.57, 1.36)             | 0.78 (0.60, 1.01)         |
| ≥$60,000                   | 1.00 (referent)               | 1.00 (referent)           |
| Time after start of HU therapy (IRR for 25% increase) | 1.10 (1.03, 1.17) | 1.26 (1.22, 1.30) |
| Age (IRR for 1 year increase) | 1.00 (0.98, 1.02) | 1.02 (1.01, 1.03) |

IRR: incidence rate ratio; 95% CI: 95% confidence interval; RUCA: rural-urban commuting area.

*Urban area with at least 50,000 residents.

**Urban area with between 10,000 and 50,000 residents.
It is possible that we experienced migration between distance groups during the time-frame of our study, resulting in misclassification of distance. We could not measure this directly in the study, which is a limitation. However, we evaluated this potential concern with a bias analysis. Results of the bias analysis indicate that high levels of misclassification of distance (30.0%) could not explain all of the observed association between distance and hospitalizations.

Migration in and out of the St. Jude catchment area is an additional concern that could not be measured in this study due to the limitations of the data available. We found that 90.0% of the patients included were seen within 18 months of the start and within 18 months of the end of their eligible follow-up time. We would assume some non-compliance with scheduled visits which could be as infrequent as twice per year. Therefore, we estimate the number of study patients migrating in or out of the St. Jude catchment area at well below 10.0% and not likely to have a substantial impact on the observed results.

Several additional limitations of this study should be noted. It is unclear if the association between distance and rates of hospitalization would extend to types of sickle cell disease other than Hb SS. The retrospective nature of the study limited the data available for analyses. For example, we could not study potential confounding factors such as the mode of transportation to the sickle cell center, availability of a car, number of children or other dependents in the household, and access to home pain medications. Most indicators of the severity of hospitalizations such as pain scores and length of stay were not available. However, we found no association between hospitalization rates for ACS and distance from St. Jude. At St. Jude, a large clinical cohort study is currently in progress that will collect data comprehensively on treatments, clinical outcomes, demographics, and patient migration patterns over time (NCT#02098863). This study will enable more comprehensive evaluations of this and other related research questions in the future.

Other factors besides distance may also affect hospitalization rates in patients who live ≥35 miles from St. Jude. Patients in a rural setting may be more likely to manage pain crises and other acute events at home because of a lack of satisfaction with local health services due to perceived stigmatization or providers who are less knowledgeable about sickle cell disease. Potential cultural and socioeconomic differences in rural vs. urban hospitalization rates in sickle cell disease are areas for future study. It should also be noted that St. Jude is unique in its ability to provide full transportation reimbursement, parking, meals and, when necessary, housing for every visit at no cost to the patient. If distance is a true barrier for St. Jude patients, it could be much stronger for patients in other regions where financial barriers are not negated.

Consistent and comprehensive care is paramount to achieving the best possible health for children with sickle cell disease. Despite aggressive efforts to eliminate barriers to care, we still found that greater distance from a sickle cell center was associated with fewer hospitalizations and routine clinic visits. This difference could not be explained by other factors measured in our study. Additional research is needed to identify the specific factors contributing to this finding and to develop targeted interventions to minimize the effect of distance on care for patients with sickle cell disease.

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Supplementary material available online
Supplemental Table 1