



Transcranial Doppler Screening Adherence among Children with Sickle Cell Anemia Seen in the Emergency Department

Julie K. Weisman, MD^{1,*}, Carrie E. Diamond, MD^{1,*}, Sarah Kappa, MD¹, and Robert Sheppard Nickel, MD, MSc^{1,2}

Objective To evaluate adherence to annual transcranial Doppler ultrasound (TCD) screening to prevent stroke among patients with sickle cell anemia (SCA) seen in the emergency department (ED).

Study design This retrospective chart review included patients with SCA seen at a large pediatric ED over 64 weeks. Patients who did not need a TCD (age <2 or ≥16 years, on chronic transfusions, history of an inadequate TCD) or were not followed at the study institution were excluded. Patients who had received a TCD in the last 12 months (TCD adherent) were compared with patients who had not (TCD nonadherent).

Results During the study period, 257 patients with SCA in need of an annual TCD were identified and 63 patients (25%) had not received an annual TCD, including 19 patients (7%) who had never had a TCD. All TCD adherent patients had a clinic visit in the last year compared with 75% of TCD nonadherent patients, $P < .0001$. The mean interval time since the last hematology clinic appointment from the ED encounter was greater for the TCD nonadherent group: 70 vs 270 days, $P < .0001$. Demographics including markers of socioeconomic status were not significantly different between the 2 groups.

Conclusions Patients with SCA who present to the ED and are nonadherent to TCD screening guidelines are less likely to have had a recent hematology clinic visit. Future interventions to improve screening for stroke in SCA should target this patient population seen in the ED but not clinic. (*J Pediatr* 2020;217:172-6).

Sickle cell anemia (SCA) is a major cause of stroke in children leading to serious morbidity and mortality. Historically, without disease modifying therapy, 11% of children with SCA suffered an overt stroke by age 20 years.¹ Transcranial Doppler ultrasound (TCD) measurements of the large intracranial vessels' blood flow velocities are effective in identifying children with SCA at highest risk for stroke. Children with an "abnormal" TCD (velocities greater than 200 cm/second using the nonimaging technique) have a greater than 40% risk of developing an overt stroke.² The landmark Stroke Prevention Trial in Sickle Cell Anemia demonstrated that chronic red blood cell (RBC) transfusion decreases the risk of overt stroke by more than 90% in children with an abnormal TCD, thus, establishing the utility of TCD screening.³ In clinical practice, TCD screening and chronic transfusion has successfully decreased the incidence of first overt strokes in children with SCA.^{4,5} Studies have shown that hydroxyurea treatment decreases elevated TCD velocities and also offers stroke protection.⁶⁻¹⁰ Strict surveillance with TCDs is, thus, essential to identify children with SCA at increased risk for stroke to ensure they receive disease modifying therapy to prevent stroke.

The National Heart, Lung, and Blood Institute Evidence-Based Management of Sickle Cell Disease (SCD) Expert Panel Report strongly recommends an annual TCD for all patients with SCA from age 2 to 16 years.⁷ Implementation of this important screening recommendation around the country is not ideal; various studies have reported adherence rates ranging from 10% to 79%, with most reporting that less than 50% of children receive an annual TCD.¹¹⁻¹⁶ In studying adherence to TCD screening, a significant finding previously described is that "missed opportunities" for TCD screening (defined as having an SCA-related outpatient visit with no TCD that same year) occur frequently.¹⁶ Recognizing this, adherence to TCD screening is routinely evaluated in all patients with SCA seen in our hematology clinic, and patients who have not had their annual TCD are scheduled for a TCD. Despite this effort, we hypothesized that a substantial number of patients remain nonadherent to TCD screening who do not attend clinic regularly.

As patients with SCA who do not attend hematology clinic may still frequent the emergency department (ED), evaluation of TCD screening rates among patients seen in the ED may be especially informative. This study describes adherence to TCD

ADI	Area deprivation index
CNHS	Children's National Health System
RBC	Red blood cell
SCA	Sickle cell anemia
SCD	Sickle cell disease
SES	Socioeconomic status
TCD	Transcranial Doppler ultrasound

From the ¹Division of Hematology, Children's National Health System; and ²George Washington University School of Medicine and Health Sciences, Washington, DC

*Contributed equally.

The authors declare no conflicts of interest.

0022-3476/\$ - see front matter. © 2019 Elsevier Inc. All rights reserved.
<https://doi.org/10.1016/j.jpeds.2019.10.049>

screening guidelines among a large cohort of patients with SCA seen in the ED and risk factors for nonadherence. We specifically tested the hypothesis that patients nonadherent to TCD screening are less likely to have had a recent hematology clinic visit.

Methods

We conducted a retrospective chart review of all patients with SCD seen at the Children's National Health System (CNHS) ED between February 1, 2016 and April 23, 2017. Patients with SCD were identified through an electronic ED clinical registry that includes all ED patient encounters using *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* codes. SCD genotype was then determined by chart review. This cohort was originally studied as part of our Quick Start Hydroxyurea Project.¹⁷ For the current study, only patients in need of an annual TCD were included: patients with SCA (genotypes hemoglobin SS or $S\beta^0$ thalassemia) age 2-16 years. SCA genotype was verified by review of a hemoglobin electrophoresis result. Patients already on chronic RBC transfusions or with prior documentation of a technical problem preventing TCD screening (skull bone window inadequate to visualize vessels) were excluded. Patients with SCA that were not established CNHS hematology patients were also excluded given that we would not be able to determine if they had a TCD in the last 12 months via chart review. Patients were defined as established CNHS patients if they had a prior hematology clinic visit at our institution and no documentation of establishing care with another outside hematologist. The CNHS Institutional Review Board approved this study with a waiver of informed consent.

CNHS TCD Screening Protocol

CNHS follows the most recent National Heart, Lung, and Blood Institute guidelines to screen patients with SCA between the age of 2 and 16 years with an annual TCD (every 12 months) per a clinical care, not research, protocol. TCDs are performed in radiology which is located in the same building as the CNHS hematology clinic but on a different floor. TCDs are attempted to be scheduled the same day as a hematology clinic visit.

Area Deprivation Index Evaluation

As a measure of socioeconomic status, an area deprivation index (ADI) score was determined for each patient by inputting their home address into an online Neighborhood Atlas (<https://www.neighborhoodatlas.medicine.wisc.edu/mapping>). The ADI score (0-100) is a validated measure of neighborhood disadvantage considering income, education, employment, and housing quality using 2009-2013 American Community Survey data.^{18,19} A higher ADI score indicates more disadvantage.

Statistical Analyses

For analysis, patients were classified as "TCD adherent" if they had a TCD in the previous 12 months from the ED visit. The first ED visit during the study time period was used for patients with multiple ED visits. Continuous variables were compared using the 2-sample t test. Categorical data were compared with the Fisher exact test or χ^2 test as appropriate. Multivariate analysis was performed via logistic regression. Statistical calculations were performed with SAS University Edition (SAS Institute Inc, Cary, North Carolina) and graphics created using GraphPad Prism v 8.1 (GraphPad Software, La Jolla, California).

Results

During the 64-week study period, a total of 739 patients with a SCD diagnosis (all genotypes) were seen in the CNHS ED. For further study in order to identify only patients age 2-16 years with a SCA genotype already established at our institution in need of a screening TCD, 482 patients were excluded (**Figure 1**). This included 9 patients who had a SCD diagnosis in the ED database but upon medical record review did not actually have the disease. Among the 64 excluded patients who were not established CNHS hematology patients, 7 patients had no hematologist as they were recent immigrants. The final study cohort, thus, involved a total of 257 patients. Among this group, 16 patients had not been seen in the CNHS hematology clinic within the year prior to the ED encounter, but all of these patients subsequently had a CNHS hematology clinic visit (they had been lost to regular follow-up but were still followed by our institution).

Adherence to TCD Screening

Among the 257 patients in the study cohort, 63 patients (25%) had not received a needed TCD in the last year. In this TCD nonadherent group, 44 patients had a previous TCD a median of 1.4 years (range 1.02-11.5 years) before the ED encounter, whereas 19 patients (7% of the study cohort) had never had a TCD. When excluding patients age 2-2.99 years ($n = 33$) in whom a first TCD may have been planned soon after the ED encounter, a similar proportion of patients had not received a TCD in the last year (53 of 224, 24%), but a slightly smaller proportion had never had a TCD (9 of 224, 4%).

TCD Adherence Was Associated with Hydroxyurea Use and Clinic Attendance

Table 1 reports the comparison of the patients who had a TCD in the last year (TCD adherent) with those who did not (TCD nonadherent). The age and sex distributions of these 2 groups were similar. To evaluate socioeconomic status, ADI and health insurance coverage were compared. Patients with private health insurance had a significantly lower mean ADI (**Figure 2**; available at www.jpeds.com), but both of these variables were not significantly different

739 patients with SCD diagnosis seen in ED during study period

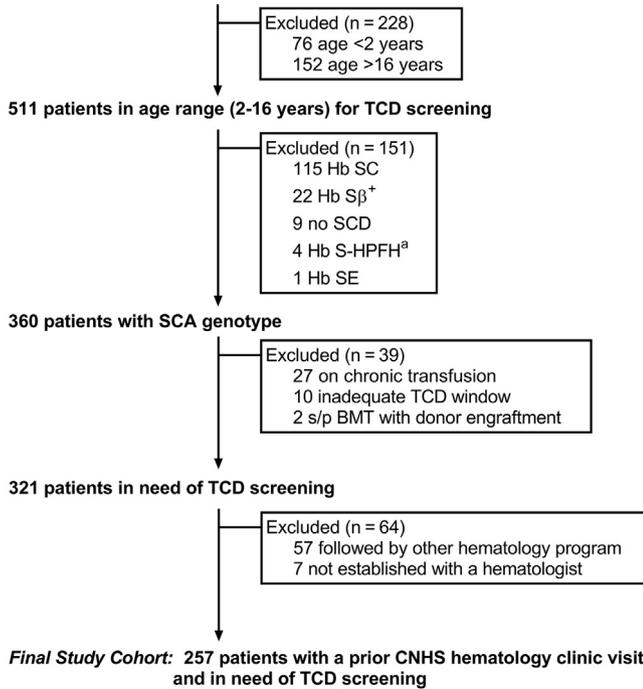


Figure 1. Flow diagram of patients included in the final study cohort. *BMT*, bone marrow transplant; *Hb*, hemoglobin; *HPFH*, deletional hereditary persistence of fetal hemoglobin; *s/p*, status post. ^aPatients were classified as Hb S-HPFH only if they had genetic testing that confirmed a deletion in the beta-globin gene cluster.

among the TCD adherent vs nonadherent groups. Patients adherent to TCD screening were much more likely to be taking hydroxyurea (67%) than nonadherent patients (29%), $P < .0001$. A recent hematology clinic visit was also significantly associated with TCD screening. All patients in the TCD adherent group had a clinic visit in the last year, compared with only 75% of the nonadherent group, $P < .0001$. The mean interval time since the last hematology clinic visit from the ED encounter was greater for TCD nonadherent patients, 70 days vs 270 days, $P < .0001$ (Figure 3). On multivariate analysis, only the number of days since the last hematology clinic visit was significantly associated with TCD adherence (Table II).

Table I. Univariate analysis of variables associated with adherence to TCD screening

Variables	TCD adherent n = 194	TCD nonadherent n = 63	P value
Age, mean y (SD)	7.8 (3.8)	7.9 (4.5)	.77
Sex, male	88 (45%)	29 (46%)	.93
Private health insurance	50 (26%)	14 (22%)	.57
ADI score, mean (SD)	31.9 (23.4)	36.2 (27.8)	.23
Number of ED visits in last y, mean (SD)	2.0 (2.8)	1.3 (1.9)	.07
Hydroxyurea use	130 (67%)	18 (29%)	<.0001
Hematology clinic visit in last y	194 (100%)	47 (75%)	<.0001

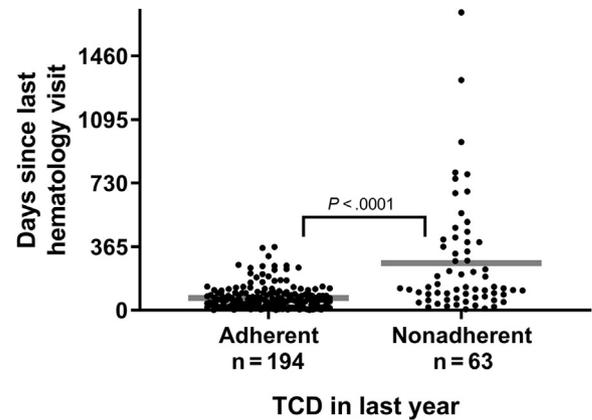


Figure 3. Comparison of time interval since last hematology clinic visit among patients adherent and nonadherent to TCD screening. The mean number of days since the last hematology clinic visit from the ED visit was significantly less for patients adherent to TCD screening compared with patients nonadherent to TCD screening (70 vs 270 days, $P < .0001$).

Follow-up of Identified Patients Who Never Had a TCD

All 19 patients identified through this study to have never had a screening TCD did subsequently have a TCD a median of 5 weeks (range 1-77 weeks) after the ED encounter. Some of these patients had a TCD only after being identified as overdue for screening through this study (SCD nurse coordinators and social workers were notified of patients still in need of a TCD at the time of chart review). Thirteen patients (68%) had a normal TCD, 3 patients (16%) had an abnormal TCD, 1 patient (5%) had a conditional TCD, and 2 patients (11%) could not be evaluated due to inadequate TCD bone windows. All 3 of the patients with an abnormal TCD result were eventually started on chronic RBC transfusion therapy for stroke prevention. The 1 patient with a conditional TCD started hydroxyurea after this result and the TCD normalized.

Discussion

This study establishes the ED as a key location for identifying an at-risk patient population overdue for SCA stroke

Table II. Multivariate analysis of variables associated with adherence to TCD screening

Variables	OR (CI)	P value
Hydroxyurea use	1.926 (0.916, 4.050)	.084
Number of days since last hematology clinic visit from the ED encounter	0.992 (0.989, 0.996)	<.0001

The variables hydroxyurea use (dichotomous variable) and days since last hematology clinic visit (quantitative variable) were included in the model as they were the only variables significant in the univariate analysis. If the interval time variable is instead expressed in years since last hematology clinic visit, the OR is 0.056 (0.015, 0.202).

prevention screening. An annual TCD is a well-established screening tool that can help prevent stroke, one of the most devastating complications of SCA. Nonetheless, we found that 1 in 4 children with SCA seen in the ED had not received a TCD in the last year. Even more concerning, 30% of those children nonadherent to TCD screening had never had a TCD. Children who were nonadherent to TCD screening were significantly less likely to have had a recent hematology clinic visit. These results demonstrate that the ED could serve as an important location for finding patients overdue for a TCD.

Similar to our results, others have also reported that children nonadherent to TCD screening are less likely to be seen in clinic for routine care. Using Tennessee Medicaid claims, Eckrich et al reported an annual TCD screening rate of 68% in 2008, and found that SCD outpatient visits were associated with better adherence to TCD screening, with patients who had no visits having especially low screening rates.¹² Also using Medicaid data from 6 other states, Reeves et al reported improved TCD screening rates (22%-44%) between 2005 and 2010, and found that an increasing number of well-child visits were associated with a higher odds of receiving a TCD.¹³ Although the finding that patients who have not had an annual TCD are also less likely to be seen in clinic is not surprising, it has critical implications when considering interventions to improve TCD screening rates. If interventions only target children who come to clinic, many children will be missed. Our study suggests that interventions targeting patients seen in the ED could identify this at-risk patient population nonadherent to both clinic follow-up and stroke screening.

Many potential barriers to TCD adherence exist including: inadequate physician ordering, families' poor understanding of its importance or fear of blood transfusions, lack of trained personnel or equipment, scheduling difficulties, inability of young children to cooperate for the test, and problems with insurance reimbursement.²⁰⁻²³ Some, but not all, prior studies have found that markers of socioeconomic status (SES) were associated with adherence to TCD screening.^{12,14,15,24} We studied ADI, a powerful tool that measures how disadvantaged is a neighborhood.^{18,19} As expected, patients who had private health insurance had a significantly lower mean ADI score (lower score = less disadvantaged). Interestingly, neither insurance status nor ADI were significantly associated with TCD adherence in this study. These markers of SES may simply fail to represent the real socioeconomic barriers related to TCD screening. Alternatively, it is possible that SES does not have a major impact on TCD adherence. Of note, CNHS has 2 full-time social workers dedicated to supporting families of children with SCD. This support likely helps mitigate socioeconomic challenges that could affect TCD adherence.

The aim of this study was not to describe outcomes of patients identified as TCD nonadherent. Nonetheless, we did ensure that every patient who had never had a TCD did eventually obtain a TCD. Among this nonadherent group, over 20% of patients were found to have an abnormal or

conditional TCD that led to starting chronic transfusion or hydroxyurea respectively for stroke prevention. Thus, identifying patients in need of TCD screening via review of patients seen in the ED is a promising strategy to ensure patients at risk for stroke receive disease modifying therapy. Protocols in the ED could be developed that evaluate in real-time if patients with SCA have had an annual TCD. This approach may not be feasible given that the ED does not focus on preventive care and TCD screening is not appropriate around the time of an acute illness. Alternatively, future work could involve regularly reviewing all patients with SCA recently seen in the ED and implementing interventions that target nonadherent patients identified through this review. Of note, this work could be helpful for overall care coordination and improving the implementation of a range of clinical guidelines. We have previously demonstrated that targeted hydroxyurea education after an ED visit increases the use of hydroxyurea.¹⁷

This study was limited to a single center; the patients studied may not be representative of all patients with SCA in the US and the study likely underestimates national nonadherence to TCD screening. Because this study was conducted at a center with a special interest in SCA stroke prevention, it is likely that adherence to TCD screening is worse at other centers with less expertise in SCA. Future work should validate the utility of reviewing TCD adherence among ED patients by studying cohorts of patients seen in different EDs around the country. An important strength of our study is that, unlike other TCD adherence studies which used medical claims data, we conducted a rigorous chart review. This chart review permitted us to exclude all patients who did not need a TCD and, thus, accurately describe the proportion of nonadherent patients.

In conclusion, in this single-center study 25% of children with SCA who presented to the ED were nonadherent to TCD screening guidelines and these patients were less likely to have had a recent hematology clinic visit. The ED could be a critical site to identify patients lost to regular clinic follow-up in need of a TCD. Interventions that specifically target this patient population will likely improve TCD screening rates and stroke prevention. ■

Submitted for publication Jun 1, 2019; last revision received Sep 17, 2019; accepted Oct 21, 2019.

Reprint requests: Robert Sheppard Nickel, MD, MSc, Division of Hematology, Children's National Health System, 111 Michigan Ave NW, Washington, DC 20010. E-mail: nickel@childrensnational.org

Data Statement

Data sharing statement available at www.jpeds.com.

References

1. Ohene-Frempong K, Weiner SJ, Sleeper LA, Miller ST, Embury S, Moohr JW, et al. Cerebrovascular accidents in sickle cell disease: rates and risk factors. *Blood* 1998;91:288-94.

2. Adams RJ, McKie VC, Carl EM, Nichols FT, Perry R, Brock K, et al. Long-term stroke risk in children with sickle cell disease screened with transcranial Doppler. *Ann Neurol* 1997;42:699-704.
3. Adams RJ, McKie VC, Hsu L, Files B, Vichinsky E, Pegelow C, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. *N Engl J Med* 1998;339:5-11.
4. McCarville MB, Goodin GS, Fortner G, Li CS, Smeltzer MP, Adams R, et al. Evaluation of a comprehensive transcranial doppler screening program for children with sickle cell anemia. *Pediatr Blood Cancer* 2008;50:818-21.
5. Fullerton HJ, Adams RJ, Zhao S, Johnston SC. Declining stroke rates in Californian children with sickle cell disease. *Blood* 2004;104:336-9.
6. Zimmerman SA, Schultz WH, Burgett S, Mortier NA, Ware RE. Hydroxyurea therapy lowers transcranial Doppler flow velocities in children with sickle cell anemia. *Blood* 2007;110:1043-7.
7. Ware RE, Davis BR, Schultz WH, Brown RC, Aygun B, Sarnaik S, et al. Hydroxycarbamide versus chronic transfusion for maintenance of transcranial Doppler flow velocities in children with sickle cell anaemia-TCD With Transfusions Changing to Hydroxyurea (TWiTCH): a multicentre, open-label, phase 3, non-inferiority trial. *Lancet* 2016;387:661-70.
8. Hankins JS, McCarville MB, Rankine-Mullings A, Reid ME, Lobo CL, Moura PG, et al. Prevention of conversion to abnormal transcranial Doppler with hydroxyurea in sickle cell anemia: a phase III international randomized clinical trial. *Am J Hematol* 2015;90:1099-105.
9. Ghafari DL, Chaturvedi S, Rodeghier M, Stimpson SJ, McClain B, Byrd J, et al. Secondary benefit of maintaining normal transcranial Doppler velocities when using hydroxyurea for prevention of severe sickle cell anemia. *Pediatr Blood Cancer* 2017;64:1-4.
10. Adegoke SA, Macedo-Campos RS, Braga JAP, Figueiredo MS, Silva GS. Changes in transcranial doppler flow velocities in children with sickle cell disease: the impact of hydroxyurea therapy. *J Stroke Cerebrovasc Dis* 2018;27:425-31.
11. Neunert CE, Gibson RW, Lane PA, Verma-Bhatnagar P, Barry V, Zhou M, et al. Determining adherence to quality indicators in sickle cell anemia using multiple data sources. *Am J Prevent Med* 2016;51: S24-30.
12. Eckrich MJ, Wang WC, Yang E, Arbogast PG, Morrow A, Dudley JA, et al. Adherence to transcranial Doppler screening guidelines among children with sickle cell disease. *Pediatr Blood Cancer* 2013;60:270-4.
13. Reeves SL, Madden B, Freed GL, Dombkowski KJ. Transcranial Doppler screening among children and adolescents with sickle cell anemia. *JAMA Pediatr* 2016;170:550-6.
14. Muntz DS, Bundy DG, Strouse JJ. Personalized reminders increase screening for stroke risk in children with sickle cell anemia. *South Med J* 2016;109:506-10.
15. Raphael JL, Shetty PB, Liu H, Mahoney DH, Mueller BU. A critical assessment of transcranial doppler screening rates in a large pediatric sickle cell center: opportunities to improve healthcare quality. *Pediatr Blood Cancer* 2008;51:647-51.
16. Reeves SL, Fullerton HJ, Cohn LM, Dombkowski KJ, Boulton ML, Braun TM, et al. Missed Opportunities for transcranial Doppler screening among children with sickle cell disease. *Clin Pediatr (Phila)* 2016;55:1093-9.
17. Pecker LH, Kappa S, Greenfest A, Darbari DS, Nickel RS. Targeted Hydroxyurea education after an emergency department visit increases hydroxyurea use in children with sickle cell anemia. *J Pediatr* 2018;201:221-8.e16.
18. Singh GK. Area deprivation and widening inequalities in US mortality, 1969-1998. *Am J Public Health* 2003;93:1137-43.
19. Kind AJ, Jencks S, Brock J, Yu M, Bartels C, Ehlenbach W, et al. Neighborhood socioeconomic disadvantage and 30-day rehospitalization: a retrospective cohort study. *Ann Intern Med* 2014;161:765-74.
20. Bollinger LM, Nire KG, Rhodes MM, Chisolm DJ, O'Brien SH. Caregivers' perspectives on barriers to transcranial Doppler screening in children with sickle-cell disease. *Pediatr Blood Cancer* 2011;56:99-102.
21. Reeves SL, Fullerton HJ, Dombkowski KJ, Boulton ML, Braun TM, Lisabeth LD. Physician attitude, awareness, and knowledge regarding guidelines for transcranial Doppler screening in sickle cell disease. *Clin Pediatr (Phila)* 2015;54:336-45.
22. Fullerton HJ, Gardner M, Adams RJ, Lo LC, Johnston SC. Obstacles to primary stroke prevention in children with sickle cell disease. *Neurology* 2006;67:1098-9.
23. Cabana MD, Kanter J, Marsh AM, Treadwell MJ, Rowland M, Stemmler P, et al. Barriers to Pediatric sickle cell disease guideline recommendations. *Global Pediatr Health* 2019;6:1-7.
24. Reeves SL, Braun TM, Dombkowski KJ, Fullerton HJ, Boulton ML, Lisabeth LD. The role of neighborhoods in the receipt of transcranial Doppler screening among children with sickle cell disease. *J Pediatric Hematol Oncol* 2015;37:269-73.

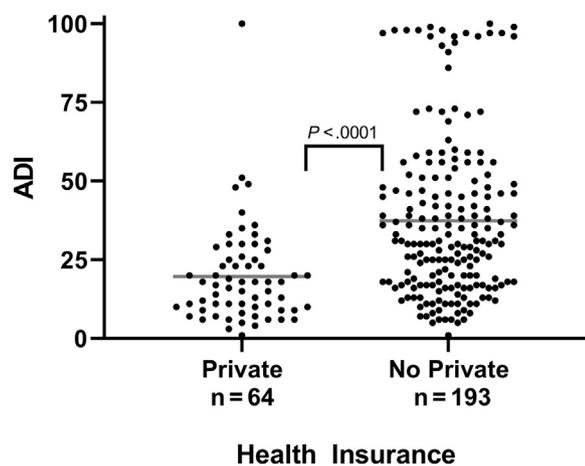


Figure 2. Comparison of ADI among patients with and without private health insurance. Patients with private health insurance had a significantly lower mean ADI score, indicating that their neighborhood was less disadvantaged than patients without private health insurance (19.7 vs 37.3, $P < .0001$).