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Association Between Hemoglobin Levels and End-Organ Damage in Sickle Cell Disease: A Retrospective Linked Primary and Secondary Care Database Analysis in England

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INTRODUCTION

- **Sickle cell disease (SCD)** is a chronic, multifaceted blood disorder that affects the oxygen-carrying protein hemoglobin (Hb). A recent systematic review found associations between low Hb from chronic hemolytic anemia in SCD and both short-term and long-term adverse outcomes, including end-organ damage (EOD).[1] Therefore, treatments with a molecular target that increase Hb by reducing hemolysis may improve patients' acute symptoms while reducing the risk for long-term disease-related effects known to contribute to morbidity and mortality.

OBJECTIVE

- This study aims to ascertain the association between Hb level variation and EOD and clinical conditions typically associated with SCD (stroke, pulmonary hypertension, chronic kidney disease [CKD], end-stage renal disease [ESRD], leg ulcers, and pneumonia) in a real-world data set.

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METHODS

- The Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES) databases in England were used to identify retrospective linked data for patients with SCD and Hb levels (April 1, 2007 to March 31, 2019). Recurring Hb results in any 90-day period were averaged. Logistic regressions were adjusted with demographic and clinical variables and used to determine odds ratios (ORs) of developing each EOD outcome or clinical complication. ORs were adjusted to take into account explanatory variables that may confound the association between Hb levels and EOD. Both adjusted and unadjusted ORs were reported to demonstrate the association before and after confounding. Paired AUC-ROC (area under the curve–receiver operator characteristic) comparisons were performed using the Delong method between the unadjusted and adjusted models. Patients with preexisting chronic EOD (pulmonary hypertension, chronic kidney disease [CKD], and kidney failure) were excluded from the corresponding models.

RESULTS

- Of 12,133 patients identified with SCD, 6964 (57%) had Hb results recorded in primary care (CPRD). There was no difference in descriptive statistics (**Table 1**) or evidence of selection bias for patients with and without Hb. The logistic regression models indicated that a **1 g/dL increase in Hb among patients with SCD was associated with a statistically significant (P<0.001) decrease in $OR_{adjusted}$ for clinical complications** (**Figure**). Adjusting for demographic and clinical covariates led to increased effect size (lower ORs).
- The model predicted a lower risk for stroke ($OR_{adjusted}$=0.89) after adjusting for clinical and demographic factors. Increased Hb was also associated with decreased risk of respiratory-related events. Pulmonary hypertension had the strongest effect with the most robust model ($OR_{adjusted}$ of 0.66), and for pneumonia (proxy for acute chest syndrome), $OR_{adjusted}$ was 0.77. For renal insufficiency, ORs for developing CKD or end-stage renal disease were significantly lower than 1 ($OR_{adjusted}$=0.73 and $OR_{adjusted}$=0.75, respectively).
- The estimated AUC-ROCs suggest that the adjusted models were more robust in stroke, pulmonary hypertension, and CKD. These findings did not change when testing for other covariates, such as deep vein thrombosis (**Table 2**).

Table 1. Baseline Characteristics of SCD Patients With Hemoglobin (Hb) Values

			SCD with Hb
Total patients			6964
Age at index, years		Mean (SD)	32.69 (18.36)
Gender	Female	Count (%)	4364 (62.67)
Follow-up (months) from index date to the last observation date		Mean (SD)	83.06 (42.47)
Charlson comorbidity score distribution (at baseline), n (%)		0	6239 (89.59)
		1-4	708 (10.17)
		5-9	17 (0.24)
Distribution of deprivation quintiles (at baseline), n (%)		1 (Least deprived)	388 (5.57)
		2	527 (7.57)
		3	986 (14.16)
		4	2113 (30.34)
		5 (Most deprived)	2944 (42.27)
		Unknown/unstated deprivation	6 (0.09)
Ethnic group, n (%)		Mixed	350 (5.03)
		Black	5132 (73.69)
		White	557 (8)
		South Asian	185 (2.66)
		Other Asian	92 (1.32)
		Other	238 (3.42)
		Unknown	410 (5.89)

A limitation of this dataset was patients without Hb values. Descriptive statistics for these patients were assessed.
SCD, sickle cell disease; SD, standard deviation.

Figure. Adjusted Odds Ratios for Selected Clinical Complications Based on a 1 g/dL Increase of Hemoglobin in Patients With Sickle Cell Disease

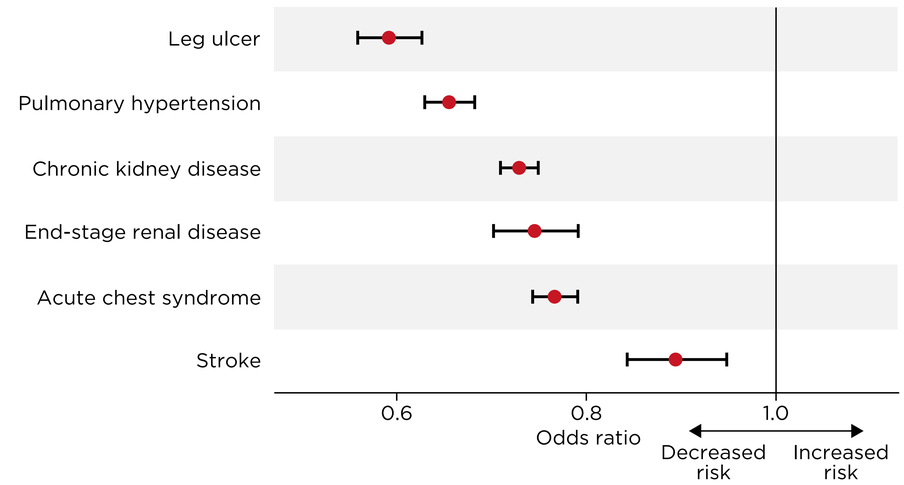

Table 2. Comparison of Model Fit for Adjusted and Unadjusted Models

	Unadjusted			Adjusted[a]			
Conditions	OR	AUC-ROC	95% CI AUC-ROC	OR	AUC-ROC	95% CI AUC-ROC	Comparison AUC-ROC
Leg ulcer	0.69	0.54	0.68-0.71	0.6	0.57	0.56-0.58	<0.001
Pulmonary hypertension	0.74	0.74	0.73-0.76	0.66	0.84	0.82-0.85	<0.001
Chronic kidney disease	0.96	0.63	0.62-0.63	0.73	0.79	0.78-0.80	<0.001
End-stage renal disease	0.83	0.77	0.76-0.78	0.75	0.64	0.62-0.66	<0.001
Pneumonia	0.79	0.69	0.62-0.64	0.77	0.64	0.63-0.65	0.098
Stroke	0.99	0.63	0.53-0.55	0.89	0.77	0.76-0.78	<0.001

[a]**Clinical variables** were selected based on clinical opinion and literature review and assessed with a bivariate analysis. They included hypertension, erythropoiesis-stimulating agent use, valve disorders — aortic stenosis and mitral regurgitation, oral contraceptive pill, atrial fibrillation, iron deficiency, pulmonary embolism, deep vein thrombosis, splenectomy, diabetes, and CKD. **Demographic variables** included age at first Hb reading, gender, ethnic group, index of multiple deprivation, body mass index, current alcohol and smoking status, and region of England.
AUC-ROC; area under the curve-receiver operator characteristic; CI, confidence interval; Hb, hemoglobin; OR, odds ratio.

CONCLUSIONS

- **Among patients with SCD, an increase in Hb of 1 g/dL was associated with a statistically significant reduction in risk for 6 common EOD outcomes and clinical complications.**
- The results were obtained from a representative **real-world evidence data set** analyzed over a 12-year period, which was sufficient to observe EOD events, and are **generalizable** to the UK and similar populations. Our findings **support the use of therapeutics that increase Hb** by reducing hemolysis in patients with SCD to protect against deleterious organ damage.

REFERENCE

1. Ataga KI, Gordeuk VR, Agodoa A, Colby JA, Gittings K, Allen IE. Low hemoglobin increases risk for cerebrovascular disease, kidney disease, pulmonary vasculopathy, and mortality in sickle cell disease: A systematic literature review and meta-analysis. *PloS One.* 2020;15(4):e0229959.

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DISCLOSURES

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