Relationships Among Sickle Cell Disease Complications and Their Implications for Cost-Effectiveness Modeling for Therapies With Curative Intent

Olivia M. Dong,[1] Molly Purser,[1]* William L. Herring,[1] Dee Dee Mladsi,[1] Meghan Gallagher,[2] Anjulika Chawla,[2] Jennifer W. Leiding,[2] Biree Andemariam[3]

[1] RTI Health Solutions, Research Triangle Park, NC, United States; [2] bluebird bio, Somerville, MA, United States; [3] University of Connecticut Health, Farmington, CT, United States

* Affiliation during study conduct

SUPPLEMENTAL MATERIALS

Supplemental Table 1. Characteristics of the Studies Included in the Structured Review

No.	Citation	Genotype	Population	Country	Complication	Event associated with VOC	Event	Method	Study quality rating (high, moderate, low)
1	Adegoke SA, Kuti BP, Omole KO, Smith OS, Oyelami OA, Adeodu OO. Acute chest syndrome in sickle cell anaemia: higher serum levels of interleukin-8 and highly sensitive C-reactive proteins are associated with impaired lung function. Paediatr Int Child Health. 2018 Nov;38(4):244-50.	HbSS	Pediatric; range, 6-15 years old (N = 76) Patients receiving HU, chronic transfusion, or vitamin D supplements were excluded	Nigeria	Lung dysfunction (abnormal FEV_1, FVC, and FEV_1/FVC)	NA	ACS	Logistic regression	Moderate

No.	Citation	Genotype	Population	Country	Complication	Event associated with VOC	Event	Method	Study quality rating (high, moderate, low)
2	Adesina O, Brunson A, Keegan THM, Wun T. Osteonecrosis of the femoral head in sickle cell disease: prevalence, comorbidities, and surgical outcomes in California. Blood Adv. 2017 Jul 11;1(16):1287-95.	NR	Adult and pediatric; California's Office of Statewide Planning and Development discharge databases (1991-2013) (N = 6,237)	US	AVN	NA	ACS	Multivariable Cox proportional hazards regression	High
3	Agarwal MA, Shah M, Patel B, Nolan VG, Reed GL, Oudiz RJ, et al. Association between pulmonary hypertension and clinical outcomes in hospitalized patients with sickle cell disease. Am J Respir Crit Care Med. 2018;198(4):534-7.	All	National Inpatient Sample database study of adult patients ≥ 18 years of age who were hospitalized	US	Pulmonary hypertension	NA	Stroke, ACS, VTE	Multivariate logistic and linear regression models	High
4	Akinyoola AL, Adediran IA, Asaleye CM, Bolarinwa AR. Risk factors for osteonecrosis of the femoral head in patients with sickle cell disease. Int Orthop. 2009 Aug;33(4):923-6.	HbSS (n = 41) HbSC (n = 10)	Adult and pediatric; with AVN; mean age, 23.7 years Without AVN; mean age, 21.6 years	Nigeria	Osteonecrosis	NA	VOC	*t*-tests	Moderate

No.	Citation	Genotype	Population	Country	Complication	Event associated with VOC	Event	Method	Study quality rating (high, moderate, low)
5	Anele UA, Burnett AL. Erectile dysfunction after sickle cell disease-associated recurrent ischemic priapism: profile and risk factors. J Sex Med. 2015 Mar;12(3):713-9.	NR	Adult and pediatric males with recurrent ischemic priapism (N = 95) With SCD (n = 40) compared with without SCD (n = 19)	US	Erectile dysfunction	NA	Priapism	Logistic regression used to determine odds ratios	Moderate
6	Anim SO, Strunk RC, DeBaun MR. Asthma morbidity and treatment in children with sickle cell disease. Expert Rev Respir Med. 2011 Oct 1;5(5):635-45.	All	Pediatric Review article	NA	Asthma	NA	ACS	NA (review article)	NA
7	Bailey M, Abioye A, Morgan G, Burke T, Disher T, Brown S, et al. Relationship between vaso-occlusive crises and important complications in sickle cell disease patients. Presented at the American Society of Hematology; 5-8 December 2019. Virtual.	NR	Adults (≤ 16 years of age); mean age, 37.1 years (N = 15,076)	UK	AVN, cholelithiasis (gallstones) cardiomegaly, chronic kidney disease, pulmonary hypertension, central nervous system complications (hemorrhage, infarct, and infection), cellulitis, hyposplenism, osteomyelitis, sepsis	Priapism, ACS, acute kidney injury	VOC	Marginal structural models, pooled logistic regressions	High

No.	Citation	Genotype	Population	Country	Complication	Event associated with VOC	Event	Method	Study quality rating (high, moderate, low)
8	Bernaudin F, Verlhac S, Freard F, Roudot-Thoraval F, Benkerrou M, Thuret I, et al. Multicenter prospective study of children with sickle cell disease: radiographic and psychometric correlation. J Child Neurol. 2000 May;15(5):333-43.	HbSS (n = 155) $HbS\beta^0$ (n = 8) $HbS\beta^+$ (n = 3) HbSC (n = 7)	Pediatric; mean age, 10.2 ± 3.2 years; range, 5-15 years (N = 173)	France	Neurocognitive impairment	NA	Stroke	Univariate analysis, Wilcoxon paired tests Fisher's exact test, multivariate analysis	Moderate
9	Boyd JH, Macklin EA, Strunk RC, DeBaun MR. Asthma is associated with acute chest syndrome and pain in children with sickle cell anemia. Blood. 2006 Nov 1;108(9):2923-7.	HbSS (n = 291)	Pediatric; enrolled in the CSSCD before 6 months and followed beyond age 5 years	US	Asthma	NA	ACS, VOC	Generalized linear models	Moderate
10	Boyd JY, Macklin EA, Strunk RC, DeBaun MR. Asthma is associated with increased mortality in individuals with sickle cell anemia. Haematologica. 2007;92(8):1115-8.	HbSS (n = 1,963)	Adult and pediatric; Patients enrolled in the CSSCD, excluding those who died before the age of 5 or for whom follow-up ended before the age of 5	US	Asthma	NA	ACS, renal insufficiency	Multivariable Cox regression	High

No.	Citation	Genotype	Population	Country	Complication	Event associated with VOC	Event	Method	Study quality rating (high, moderate, low)
11	Bradt P, Spackman E, Synnott P, Chapman R, Beinfeld M, Rind D, et al. Crizanlizumab, voxelotor, and l-glutamine for sickle cell disease: effectiveness and value. 2020. Available at: https://icer-review.org/material/sickle-cell-disease-draft-evidence-report/ Accessed 15 September 2020.	NA	Adult and pediatric patients eligible for treatment with crizanlizumab, voxelotor, and l-glutamine	US	Pulmonary hypertension, Heart failure, CKD	ACS, MI, acute kidney injury/renal infarction, stroke	VOC	NA (ICER report)	NA
12	Cintho Ozahata MC, Page GP, Guo Y, Ferreira JE, Dinardo CL, Carneiro-Proietti AB, et al. Clinical and genetic predictors of priapism in sickle cell disease: results from the Recipient Epidemiology and Donor Evaluation Study-III Brazil Cohort Study. J Sex Med. 2019 Dec 1;16(12):1988-99.	HbSS (n = 931) HbSβ^0 (n = 42) HbSC (n = 295) HbSβ$^+$ (n = 42) Other (n = 3)	REDS-III; Adult and pediatric; age range, 0-77 years (N = 1,314)	Brazil	Pulmonary hypertension, AVN	NA	Priapism	Chi-square tests for categorical variables and Wilcoxon rank-sum tests for continuous variables	Moderate
13	De Castro LM, Jonassaint JC, Graham FL, Ashley-Koch A, Telen MJ. Pulmonary hypertension associated with sickle cell disease: clinical and laboratory endpoints and disease outcomes. Am J Hematol. 2008 Jan;83(1):19-25.	HbSS/HbSβ^0 (n = 77) HbSC/HbSO-Arab/ HbSβ$^+$ (n = 48)	Adults (N = 125) Symptomatic population	US	Pulmonary hypertension	NA	Leg ulcers, kidney dysfunction (proteinuria, decreased glomerular filtration rate)	Multivariate analysis	High

No.	Citation	Genotype	Population	Country	Complication	Event associated with VOC	Event	Method	Study quality rating (high, moderate, low)
14	DeBaun MR, Rodeghier M, Cohen R, Kirkham FJ, Rosen CL, Roberts I, et al. Factors predicting future ACS episodes in children with sickle cell anemia. Am J Hematol. 2014 Nov;89(11):E212-7.	HbSS HbSβ^0	Pediatric; mean age, 9.0 years; range, 4-18 years) Excluded patients on regular blood transfusions 51.6% male	US and UK	Asthma symptom and risk factors (wheezing causing shortness of breath, presence of 2 or more positive allergy skin tests)	NA	ACS	Multivariable negative binomial regressions	Moderate
15	Duckworth L, Hsu L, Feng H, Wang J, Sylvester JE, Kissoon N, et al. Physician-diagnosed asthma and acute chest syndrome: associations with NOS polymorphisms. Pediatr Pulmonol. 2007 Apr;42(4):332-8.	NR	Adult and pediatric; ages ≥ 5 years	US	Asthma	NA	ACS	Logistic regression analysis	Moderate
16	Intzes S, Kalpatthi RV, Short R, Imran H. Pulmonary function abnormalities and asthma are prevalent in children with sickle cell disease and are associated with acute chest syndrome. Pediatr Hematol Oncol. 2013 Nov;30(8):726-32.	HbSS (n = 79) HbSβ^0 (n = 3) HbSC (n = 30) HbSβ$^+$ (n = 14) HbSα-thalassemia (n = 1)	Pediatric; median age, 12 years (range, 16-18 years) (N = 127)	US	Asthma	NA	ACS	Logistic regression, presented Pearson correlation coefficients, and prevalence odds ratios	Moderate

No.	Citation	Genotype	Population	Country	Complication	Event associated with VOC	Event	Method	Study quality rating (high, moderate, low)
17	Joly P, Renoux C, Lacan P, Bertrand Y, Cannas G, Garnier N, et al. UGT1A1 (TA)n genotype is not the major risk factor of cholelithiasis in sickle cell disease children. Eur J Haematol. 2017 Mar;98(3):296-301.	HbSS (n = 150) HbSβ^0 (n = 8)	Pediatric (2-18 years old) (N = 158)	France	Cholelithiasis (gallstones)	NA	VOC, ACS	Univariate and multivariate analyses conducted	Moderate
18	Knight-Madden JM, Forrester TS, Lewis NA, Greenough A. Asthma in children with sickle cell disease and its association with acute chest syndrome. Thorax. 2005 Mar 1;60(3):206-10.	HbSS (n = 160)	Pediatric with SCD (n = 80) (median, 7.77 years; range, 5.24-9.73 years) Patients without SCD (n = 80) (median, 7.78 years; range, 5.14-10.45 years)	Jamaica	Asthma	NA	ACS	Logistic regression, chi-square test	Moderate
19	Knight-Madden JM, Forrester TS, Lewis NA, Greenough A. The impact of recurrent acute chest syndrome on the lung function of young adults with sickle cell disease. Lung. 2010 Dec;188(6):499-504.	HbSS	Young adults from the JSCCS (age range, 18-28 years) (n = 80) and ethnically matched controls (n = 80)	Jamaica	Reduced lung function (lower median forced vital capacity, forced expiratory volume in 1 second, and total lung capacity)	NA	ACS	Mann-Whitney U, chi-square test, multiple linear regression analysis	High

No.	Citation	Genotype	Population	Country	Complication	Event associated with VOC	Event	Method	Study quality rating (high, moderate, low)
20	Kumar R, Stanek J, Creary S, Dunn A, O'Brien SH. Prevalence and risk factors for venous thromboembolism in children with sickle cell disease: an administrative database study. Blood Adv. 2018 Feb 13;2(3):285-91.	HbSS (n = 7,332) HbSβ-thalassemia (n = 900) HbSC (n = 1,321) Unspecified (n = 901)	Pediatric; median age, 10 years (IQR, 11 years) N = 10,454	US	Chronic renal disease	NA	VTE	Multivariable logistic regression analysis	High
21	Leveziel N, Bastuji-Garin S, Lalloum F, Querques G, Benlian P, Binaghi M, et al. Clinical and laboratory factors associated with the severity of proliferative sickle cell retinopathy in patients with sickle cell hemoglobin C (SC) and homozygous sickle cell (SS) disease. Medicine (Baltimore). 2011 Nov;90(6):372-8.	HbSS (n = 629) HbSC (n = 313)	Adult and pediatric; HbSS age range: 8-64 HbSC age range: 15-66	France	Retinopathy, Chole-cystectomy	NA	ACS	Age-adjusted univariate analysis and multivariate analysis	High
22	Mesleh Shayeb A, Smeltzer MP, Kaste SC, Brown A, Estepp JH, Nottage KA. Vaso-occlusive crisis as a predictor of symptomatic avascular necrosis in children with sickle cell disease. Pediatr Blood Cancer. 2018 Dec;65(12):e27435.	HbSS/HbSβ^0 (cases, n = 15; controls, n = 79) HbSC/HbSβ$^+$ (cases, n = 11; controls, n = 48)	Pediatrics (age 6-18 years)	US	AVN	NA	VOC	Univariate regression models	High

No.	Citation	Genotype	Population	Country	Complication	Event associated with VOC	Event	Method	Study quality rating (high, moderate, low)
23	Milner PF, Kraus AP, Sebes JI, Sleeper LA, Dukes KA, Embury SH, et al. Sickle cell disease as a cause of osteonecrosis of the femoral head. N Engl J Med. 1991 Nov 21;325(21):1476-81.	HbSS (n = 1,785) HbSS homozygous (-α/-α) for α-thalassemia (n = 33) HbSS heterozygous (αα/-α) for α-thalassemia (n = 383) HbSβ^0 (n = 143) HbSC (n = 518) HbSβ^+ (n = 144)	Adult and pediatric; CSSCD population, age ≥ 5 years	US	AVN	NA	VOC	Multivariate modeling	Moderate
24	National Institute for Health and Care Excellence. Single technology appraisal, crizanlizumab for preventing sickle cell crisis in sickle cell disease [ID1406], committee papers. 2020. Available at: Available at: https://www.nice.org.uk/guidance/gid-ta10470/documents/committee-papers. Accessed 23 December 2020.	All	Adult and pediatric; patients aged 16 years old and older eligible for treatment with crizanlizumab	UK	Sepsis, gall stones, cardiac, cellulitis, osteomyelitis, pulmonary hypertension	Leg ulcers, ACS, priapism	VOC	NA (NICE appraisal)	NA

No.	Citation	Genotype	Population	Country	Complication	Event associated with VOC	Event	Method	Study quality rating (high, moderate, low)
25	Pahl K, Mullen CA. Original research: acute chest syndrome in sickle cell disease: effect of genotype and asthma. Exp Biol Med (Maywood). 2016 Apr;241(7):745-58.	HbSS (n = 51) HbSC (n = 37) HbSβ^+ (n = 11) HbSβ^0 (n = 3)	Pediatric to young adult (age range, 2-21 years)	US	Asthma	NA	ACS	Chi-square test	Moderate
26	Patterson GD, Mashegu H, Rutherford J, Seals S, Josey D, Karlson C, et al. Recurrent acute chest syndrome in pediatric sickle cell disease: clinical features and risk factors. J Pediatr Hematol Oncol. 2018 Jan;40(1):51-5.	HbSS and HbSC	Pediatrics with ACS	US	Asthma, lung dysfunction (shortness of breath)	NA	ACS	Regression (presented adjusted incident rate ratios)	Moderate
27	Powars DR, Chan LS, Hiti A, Ramicone E, Johnson C. Outcome of sickle cell anemia: a 4-decade observational study of 1,056 patients. Medicine. 2005 Nov 1;84(6):363-76.	HbSS	Adult and pediatric; N = 1,056 4 decades of observation	US	AVN, sickle chronic lung disease, renal failure	Leg ulcers	VOC	Cox regression model with time-dependent covariates	High
					Sickle chronic lung disease	NA	ACS		
28	Shah N, Bhor M, Arcona S, Halloway R. Evaluation of vaso-occlusive crises in United States sickle cell disease patients: a retrospective claims-based study. J Health Econ Outcomes Res. 2019;6(3):106-17.	All	Medicaid population, adults and children (separate models)	US	Pulmonary hypertension	ACS, stroke, pulmonary embolism, splenic seques-tration	VOC	Cox proportional hazards regression	High

No.	Citation	Genotype	Population	Country	Complication	Event associated with VOC	Event	Method	Study quality rating (high, moderate, low)
29	Strunk RC, Cohen RT, Cooper BP, Rodeghier M, Kirkham FJ, Warner JO, et al. Wheezing symptoms and parental asthma are associated with a physician diagnosis of asthma in children with sickle cell anemia. J Pediatr. 2014 Apr;164(4):821-6.e1.	HbSS or HbSβ^0	Pediatrics (aged 4-18 years) (N = 187)	US and UK	Asthma	NA	ACS	Multivariable analysis	Moderate
30	Tofovic DS, Al-Kindi SG, Oliveira G, Schilz R, Little J, Ginwalla M. Sickle cell disease and risk of heart failure. J Cardiac Fail. 2017;23(8):S77.	HbSS (n = 15,500)	Age range of cohort not reported; record data from 26 major integrated healthcare systems across the US Compared HbSS to a matched-control population	US	Heart failure	NA	MI	Regression analyses	Moderate
31	van Beers EJ, van Tuijn CF, Mac Gillavry MR, van der Giessen A, Schnog J-JB, Biemond BJ, et al. Sickle cell disease-related organ damage occurs irrespective of pain rate: implications for clinical practice. Haematologica. 2008;93(5):757-60.	HbSS (n = 59) HbSβ$^+$ (n = 5) HbSC (n = 29) HbSβ^0 (n = 11)	Adult sickle cell patients visiting the Department of Haematology of the Academic Medical Center in Amsterdam	The Nether-lands	Cholelithiasis, AVN, iron overload	Priapism, ACS	VOC	Spearman rank test	Moderate

No.	Citation	Genotype	Population	Country	Complication	Event associated with VOC	Event	Method	Study quality rating (high, moderate, low)
32	Willen SM, Rodeghier M, Strunk RC, Bacharier LB, Rosen CL, Kirkham FJ, et al. Aeroallergen sensitization predicts acute chest syndrome in children with sickle cell anaemia. Br J Haematol. 2018 Feb;180(4):571-7.	HbSS (n = 165)	Pediatric; age range, 4-18 years	US and UK	Lung dysfunction (wheezing leading to shortness of breath)	NA	ACS	Multivariable regression	High
33	Yu T, Campbell T, Ciuffetelli I, Haywood C Jr, Carroll CP, Resar L, et al. Symptomatic avascular necrosis: an understudied risk factor for acute care utilization by patients with SCD. South Med J. 2016 Sep;109(9):519-24.	HbSS (126/174; 72.4%)	Adults with AVN (n = 87) Sex and age-matched cohort with SCD and without AVN (n = 87) Mean age, 41 years (range, 24-71)	US	AVN	NA	ACS	Bivariate analysis and multivariate regression	Moderate
34	van Tuijn CF, Schimmel M, van Beers EJ, Nur E, Biemond BJ. Prospective evaluation of chronic organ damage in adult sickle cell patients: a seven-year follow-up study. Am J Hematol. 2017;92(10):E584-90.	HbSS/HbSβ° (n = 60) HbSC/HbSβ° (n = 35)	Adults visiting outpatient clinic Median age, 37 years	The Nether-lands	NA	ACS	VOC	Spearman rank test	Moderate

ACS = acute chest syndrome; AVN = avascular necrosis; EMR = electronic medical record; FVC = forced vital capacity; HR = hazard ratio; HU = hydroxyurea; ICER = Institute for Clinical and Economic Review; IQR = interquartile range; MA = meta-analysis; MI = myocardial infarction; NA = not applicable; NICE = National Institute for Health and Care Excellence; NR = not reported; SCD = sickle cell disease; SLR = systematic literature review; UK = United Kingdom; US = United States; VOC = vaso-occlusive crisis; VTE = venous thromboembolism.

Note: Study quality ratings were not applicable for health technology assessments without original research and review articles.