Modelling Long-Term Clinical Outcomes of Patients With Sickle Cell Disease With Recurrent Vaso-Occlusive Crises in the United States

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INTRODUCTION

- Sickle cell disease (SCD) is a rare hereditary blood disorder affecting ~100,000 individuals in the United States, characterized by the expression of abnormal sickle hemoglobin[1-3]
- Acute and chronic complications are driven by vaso-occlusion, hemolysis, and vasculopathy associated with the disease, and lead to higher mortality in patients with SCD[1-3]
- Vaso-occlusive crises (VOCs), caused by blockages of blood vessels, are a hallmark clinical manifestation of SCD and lead to the development of acute and chronic organ complications[1-3]
- Patients with SCD with recurrent VOCs experience multi-organ failure due to repeated tissue injury and damage, including to the heart, lungs, brain, kidneys, and bones/joints[1-3]
- Life expectancy estimates for patients with SCD range widely, from the early 40s to 50s, and depend highly on whether patients experience acute complications and chronic organ failure[4,5]
- Despite some evidence addressing life expectancy and clinical complications in SCD, long-term clinical outcomes remain unknown in patients with SCD with recurrent VOCs

OBJECTIVE

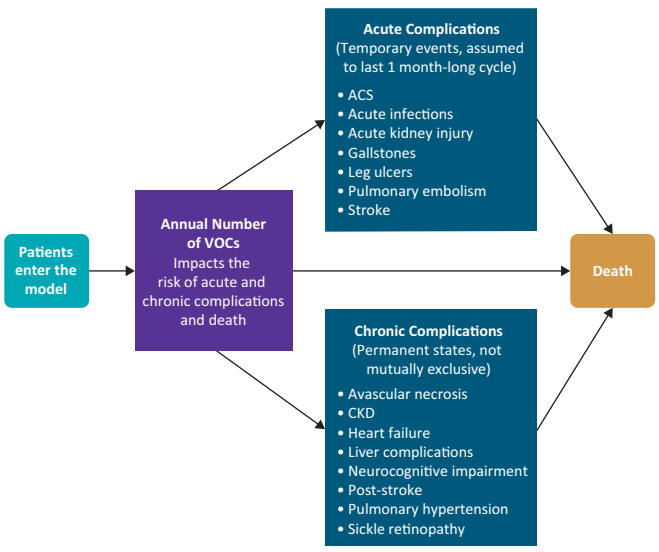
- To develop a health care decision analytic model that predicts long-term clinical outcomes and survival of patients with SCD with recurrent VOCs in the United States

METHODS

Model Overview

- A Markov cohort model was developed to estimate the life expectancy and lifetime prevalence of clinical complications in patients with SCD with recurrent VOCs in the United States
  - The model framework is similar to those used in published models of patients with SCD[6,7] (**Figure 1**)
  - The Markov model structure was selected based on the results of previous analyses, which concluded that an individual-level microsimulation required significant additional complexity which was unnecessary when modelling SCD[6]

Figure 1. Schematic for the SCD Markov Model



ACS, acute chest syndrome; CKD, chronic kidney disease; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

- In the model, the annual number of VOCs drive the risk of developing other acute and chronic complications
  - Acute complications, which are assumed to resolve within a 1-month cycle, include acute chest syndrome (ACS), stroke, acute infections, acute kidney injury, gallstones, pulmonary embolism, and leg ulcers
  - Chronic complications, which are assumed to be permanent once developed, include pulmonary hypertension, chronic kidney disease (CKD), avascular necrosis, neurocognitive impairment, retinopathy, heart failure, and liver complications
- Patients were assumed to receive standard of care (SoC) therapies for SCD, including hydroxyurea and red blood cell transfusions accompanied by iron chelation therapies
- Patients receiving SoC therapies were assumed to experience the same annual rate of VOCs from baseline to death

Data Sources and Model Inputs

- A cohort of patients with SCD with recurrent VOCs (mean age: 18 years; 50% female) were modelled from baseline; patients were assumed to experience a mean of 4 VOCs per year over their lifetimes[8]
- Patients were assumed to have no chronic complications at baseline
- The risks of developing SCD-related acute and chronic complications, as a function of the rate of VOCs, were informed by published literature (**Table 1**); the model combined the incidence of complications expected in the absence of VOCs with a hazard ratio in order to capture the increased risk of developing complications associated with more frequent VOCs
- Age-specific annual mortality risks for uncomplicated SCD were modified from Hassell, et al[1] to reflect increased mortality associated with VOCs and SCD-related complications (**Table 2**)

Data Sources and Model Inputs (Continued)

Table 1. Risk of Developing SCD-Related Complications

Complication	Annual Incidence When VOC = 0	Incidence HR for VOC = 1 Vs VOC = 0	Source
Acute complications	**Annual rate**		
ACS	0.003	58.67	Shah, et al[9]
Stroke	0.025	2.26	Shah, et al[9]
Acute infections[a]	0.237	2.26	Shah, et al[9]
Acute renal failure	0.014	2.2[c]	Yeruva, et al[10]
Gallstones[a]	0.033	2.26	Shah, et al[9]
Pulmonary embolism	0.013	2.82	Shah, et al[9]
Leg ulcers[a]	0.100	2.26	Singh, et al[11]
Chronic complications	**Annual risk, %**		
Pulmonary hypertension	0.81	4.12	Shah, et al[9]
CKD	1.43	3.00[c]	Bradt, et al[7]
Avascular necrosis[b]	2.69	4.12	Shah, et al[9]
Neurocognitive impairment[b]	2.03	4.12	Cahill, et al[12]
Retinopathy[b]	0.50	4.12	Shah, et al[13]
Heart failure[b]	0.75	4.12	Bradt, et al[7]
Liver complications[b]	0.21	4.12	Moon, et al[14]

ACS, acute chest syndrome; CKD, chronic kidney disease; HR, hazard ratio; SCD, sickle cell disease; VOC, vaso-occlusive crisis.
[a]HR was assumed to be the same as that reported for stroke (2.26), given the lack of available data;
[b]HR was assumed to be the same as pulmonary hypertension (4.12), given the lack of available data;
[c]Odds ratio.

Table 2. Mortality Associated With SCD-Related Complications

Complication	Mortality HR for Complication Vs Without Complication	Source
Acute complications		
VOC	1.56	Shah, et al[9]
ACS	1.27	Elmariah, et al[15]
Acute renal failure	9.50	Yeruva, et al[10]
Pulmonary embolism	2.75	Brunson, et al[16]
Leg ulcers	1.66	Elmariah, et al[15]
Stroke	7.4% instant risk	Bradt, et al[7]
Chronic complications		
CKD	9.57	Bradt, et al[7]
Pulmonary hypertension	12.57	Bradt, et al[7]
Heart failure	12.57	Bradt, et al[7]
Liver complications	2.53	Gardner, et al[17]

ACS, Acute chest syndrome; CKD, chronic kidney disease; HR, hazard ratio; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

Model Outcomes

- The following outcomes were projected by the model:
  - Mean life expectancy
  - Mean number of VOCs, other acute complications, and chronic complications
  - Proportion of patients developing each chronic complication
- All outcomes were undiscounted

Scenario Analyses

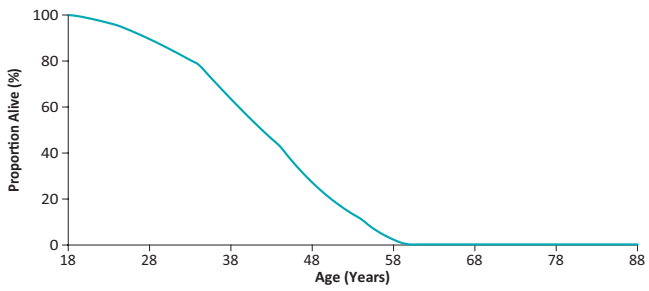
- Model parameters that were varied from the base case to evaluate the impact on SCD life expectancy included:
  - The annual number of VOCs, varied from 2 to 8 episodes
  - Alternative published sources to inform inputs for mortality associated with chronic complications: a hazard ratio of 3.6 for CKD[10], 2.34 for pulmonary hypertension[15], and 1.51 for heart failure[15]
  - Mortality inputs for VOCs and SCD-related complications increased/decreased by 20%

RESULTS

Base Case Results

- The cohort of patients with SCD with recurrent VOCs were followed in the model for a mean of 24.2 years (**Figure 2**), during which time they experienced a mean of 94.3 VOCs
  - Mean life expectancy was 42.2 years

Figure 2. Survival for SCD Cohort Treated With SoC Therapies



SCD, sickle cell disease; SoC, standard of care.

- Patients experienced a mean of 15.8 acute complications other than VOCs, with the most common being acute infections (8.1) (**Table 3**)
- The most common chronic complications that patients developed throughout their lifetimes were avascular necrosis (54.7%) and neurocognitive impairment (47.3%) (**Table 3**)

Table 3. Base Case Results

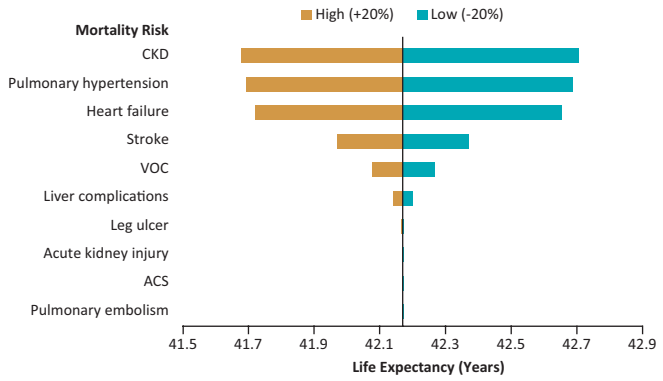
	Value
Survival, mean	
Total life years (undiscounted)	24.2
Life expectancy, years	42.2
Acute complications per patient, mean	
VOCs	94.3
Acute infection	8.1
Leg ulcer	3.4
ACS	1.4
Gallstones	1.1
Stroke	0.8
Pulmonary embolism	0.5
Acute kidney injury/failure	0.5
Proportion of patients experiencing chronic complications, %	
Avascular necrosis	54.7
Neurocognitive impairment	47.3
CKD	36.6
Pulmonary hypertension	25.0
Heart failure	23.6
Retinopathy	16.7
Liver complications	7.5

ACS, acute chest syndrome; CKD, chronic kidney disease; VOC, vaso-occlusive crisis.

Scenario Analysis Results

- When the mean number of annual VOCs was varied from 2 to 8, life expectancy was 43.9 years and 39.6 years, respectively
- When using the set of alternative sources to inform mortality inputs for chronic complications, the life expectancy estimate increased to 54.4 years
- A one-way sensitivity analysis that varied parameters by ±20% suggested that the model survival estimates were most sensitive to mortality inputs for CKD, pulmonary hypertension, and heart failure (**Figure 3**)

Figure 3. Scenario Analyses Modifying Mortality Rates



ACS, acute chest syndrome; CKD, chronic kidney disease; VOC, vaso-occlusive crisis.

Model Structure Assessment

- The use of a Markov model structure is appropriate for predicting long-term clinical outcomes in patients with SCD with recurrent VOCs; the additional complexity of utilizing an individual-level simulation was unnecessary
- This model structure is conducive to modelling the benefits of novel therapies that reduce the frequency of or eliminate VOCs in patients with SCD with recurrent VOCs
- The modelled prevalence of SCD-related complications was broadly aligned to published literature estimates[7,18-20]

LIMITATIONS

- Health care decision analytic models based solely on VOCs could oversimplify the complexity of SCD pathophysiology, given the impact of hemolysis and changes to vasculature with acute and chronic complications
- As a simplifying assumption, the modelled cohort was assumed to experience 4 VOCs per year over their lifetime; the rate of VOCs was not assumed to depend on age or other clinical characteristics
- The model did not estimate the impact of recently approved therapies for SCD on clinical outcomes; previous literature suggests that including these therapies in SoC treatment may lead to improved clinical outcomes in patients with SCD

CONCLUSIONS

- Model projections demonstrated that patients with SCD with recurrent VOCs in the United States have a reduced life expectancy and experience substantial disease burden
- An increased number of VOCs and higher rates of mortality for patients with SCD, particularly in those who developed organ complications, were key drivers in the estimates of life expectancy
- Treatments that minimize the occurrence of VOCs and reduce disease complications could improve survival and long-term outcomes in this patient population

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AUTHOR DISCLOSURES

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