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Survival in adults with sickle cell disease in a high-income setting

Kate Gardner[1,2], Abdel Douiri[3,4,5], Emma Drasar[1,2], Marlene Allman[2], Anne Mwirigi[2], Moji Awogbade[2], Swee Lay Thein[1,2*]

1. King's College London, Molecular Haematology, Division of Cancer Studies, London SE5 9NU, UK
2. King's College Hospital NHS Foundation Trust, Department of Haematological Medicine, London SE5 9RS, UK
3. Division of Health and Social Care, King's College London, London
4. NIHR Biomedical Research Centre, Guy's and St Thomas' NHS Trust and King's College London, London, UK
5. NIHR Collaboration for Leadership in Applied Health Research & Care, King's College Hospital NHS Foundation Trust, London, UK

* Present address: National Heart, Lung and Blood Institute / NIH, Sickle Cell Branch, Bethesda, USA

Correspondence:

Swee Lay Thein
Sickle Cell Branch
National Heart, Lung and Blood Institute
The National Institutes of Health
Building 10-CRC, Room 5E-5142
10 Center Drive, Bethesda, MD 20892
Office Line: +1-301-435-2345
Direct Line: +1-301-402-6699
Fax: +1-301-451-7091
Email: sl.thein@nih.gov

Kate Gardner
Molecular Haematology
King's College London
James Black Centre
125 Coldharbour Lane
London SE5 9NU;
Tel: +44-207-848-5455.
Email: kate.gardner@doctors.org.uk

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To the editor:

Survival of patients with sickle cell disease (SCD) in high-income countries has improved greatly in the last 60 years. In 1960, it was described as a "disease of childhood"[1] while 25 years later, the Cooperative Study of Sickle Cell Disease reported that 85% HbSS patients lived to adulthood. More recently, the estimate is 99% in London,[2] 97% in Paris[3], and 94% in the United States.[4]

Survival estimates have continued to improve; in 1994, the median survival for patients with HbSS/$S\beta^0$ thalassemia was estimated at 42-48 years,[5] increasing to 53-58 years in Jamaica in 2001[6] and 58 years in the USA in 2014.[7] Nonetheless, the life expectancy of patients with SCD is still shortened by more than 2 decades compared to the general population.[8-10]

The present study evaluates survival among adult patients with SCD followed at a single center in the UK. The study was an audit of clinical practice, and involved analysis of data collected in routine clinical care. All procedures followed were in accordance with the ethical standards of the Helsinki Declaration of 1975, as revised in 2008. 712 adult (16-80 years) patients with SCD at King's College Hospital, London, UK, were observed over 10 years (2004-13 inclusive) and mortality outcome identified (5268 patient-years of observation, median eight years of observation/patient).

All patients, except for one, were of African or African-Caribbean heritage. Of the 712 patients, there were 444 (62%) HbSS, 229 (32%) HbSC, 33 (5%) $HbS\beta^+$ thalassemia, and 6 (1%) $HbS\beta^0$ patients. For sub-analysis, we considered HbSS and $HbS\beta^0$ thalassemia patients as a group. The median age for HbSS/$S\beta^0$ patients was 32 years (IQR: 25-43); HbSC, 39 years (IQR: 29-48); and $HbS\beta^+$ thalassemia, 40 years (IQR: 31-58). α-globin genotypes were available in 542 (76%) patients of which 62% were αα/αα, 32% αα/α-, and 5% α-/α- genotypes. During the study period, 72 (all HbSS) patients had received hydroxyurea therapy, and 71 patients had received regular blood transfusion. We underline the low uptake of hydroxyurea therapy in our cohort. Oxygen saturations by pulse oximetry and

laboratory data collected during outpatient clinic attendance were documented. Laboratory results were averaged over the 10-year period to create a "steady state" value for each patient. The mean number of hospital admissions under hematology for each patient was calculated from the total admissions/number of observed years of admissions. Local hospitals were contacted to identify outcome in patients not seen in 2012 or 2013; despite this, 104 (14.6%) were not reviewed in 2012 or 2013. Data collection finished on 31 July 2015.

IBM SPSS Statistics 22 was used for statistical analyses. Continuous variables were log transformed where necessary to obtain normalised distributions. Kaplan Meier survival analysis considered non-fatal cases as censored at their last clinic visit. Univariate Cox regression analysis was undertaken for the HbSS/Sβ^0 subgroup only to identify risk factors for mortality. Dichotomous variables were handled as follows: α-thalassemia, default=no; sex, default=male; fetal hemoglobin (HbF) based on median split of validated HbF values (default HbF<5.5%); iron overload based on ferritin>1000µg/L, default=no; mean hospitalization rate, default ≤0.5admissions/year. We chose this cut-off based on the very skewed data distribution: it is clinically meaningful (equivalent to 1 admission every two years) and to ensure we had large enough numbers in the "high admission rate" group for statistical analyses.

During the study period, 43 of the 712 patients (6.0%) died at a median age of 42 years (IQR: 31-48). They included 33 deaths in the 450 HbSS/HbSβ^0 (7.3%) group, at median age 41 years (IQR: 30-47), and eight deaths in 229 HbSC patients (3.5%), at median age 46 years (31-72). For the HbSS/HbSβ^0 group, Kaplan Meier analysis gave an estimated median survival of 67 years (CI 55-78 years); significantly lower than in HbSC ($p<0.001$, figure 1A). For HbSS/HbSβ^0, there was a 90% estimated survival to 45 years (39-51), 80% to 51 years (CI 44-57), and 70% to 60 years (CI 51-69).

Sub-analysis was undertaken for the HbSS/HbSβ^0 subgroup; the sample size in HbSC subgroup was too small. Median survival in patients with high hospital admission rates

(>0.5 admissions/year) was 60 years (CI: 43-77), significantly lower than that in patients with low admission rates (≤0.5/year) (p=0.001, figure 1B).

Univariate Cox regression analysis (Table 1A) revealed that neither α-thalassemia nor sex were significant risk factors for death. Lack of difference in survival between the sexes may be due to the low numbers of deaths. Hospitalization frequency was a simple but strong predictor of survival in SCD; the risk of death was more than 3-fold if patients had high frequency admissions compared to those with low admission rate. Neither hydroxyurea nor blood transfusion was associated with mortality. This likely reflects both the relatively low use of these therapies in our cohort and also the disproportionate use of these therapeutic strategies in our younger patients, confounding the data. Risk of death was increased nearly 3-fold if baseline oxygen saturations were low (<95%).

For steady state laboratory results, risk of death was increased if there was: increased WBC, low baseline HbF level, higher lactate dehydrogenase (LDH), higher C-reactive protein, or iron overload (ferritin >1000ug/L). The correlation of disease severity with iron overload is likely via transfusion rate; it is unclear if iron overload in itself is an independent risk factor. For hepatic enzymes, risk of death was increased if total bilirubin, aspartate transaminase (AST) or alkaline phosphatase were raised, but alanine transaminase nor γ-glutamyl transferase affected mortality risk. This may reflect red cell rather than hepatic origin of bilirubin and AST. Conspicuously, AST provides more dramatic hazard ratios than LDH as a marker of hemolysis. Both measures of renal dysfunction (creatinine and urinary albumin creatinine ratio) demonstrated significant associations with mortality.

Multivariate Cox regression analysis (Table 1B) was based on combining variables associated with risk of death in the univariate analysis, plus sex and age at the start of the study. Variables that remained independently significant after multivariate analysis were high admission rate (>0.5/year), Ln Creatinine, and Ln Aspartate transaminase, each associated with striking hazard ratios. (Table 1B) suggesting that poor renal function, excess hemolysis, and frequent hospital admissions can all contribute independently to mortality risk in SCD.

In this retrospective analysis, we have demonstrated a high estimated survival (median 67 years) for adults with HbSS/HbSβ^0 at a single UK center, which is markedly higher than recent estimates from other institutions. We speculate the reasons: close monitoring of patients in a specialist hematology clinic, plus regular joint care with other specialists (renal, hepatology, neurology, cardiology, obstetrics and orthopedics); inpatient management by a dedicated health-care team; on-site erythrocytapheresis; and a focused "transition program" to ensure safe transition of teenagers to the adult service. Four of the 43 deaths were in patients under the age of 25 years, one from hemo-pericardium due to stab wound, one from cerebral hemorrhage, and two from fulminant hepatic failure. We did not assess the socio-economic class of each patient, but they were from a broad spectrum of social backgrounds. All these features are similar to other large sickle centers in the UK.

We acknowledge some study limitations. As an adult-only study, exclusion of pediatric patients may have inflated survival estimates; however, the vast majority of SCD patients reach adulthood in the UK.[2] We concede that we did not model for those "lost in transition" between pediatric and adult care. However, all 100 patients who turned 19 in 2008-2013 inclusive (data from the King's Pediatric Sickle database) have been seen in the adult clinic. We also recognize some missing data for those not reviewed at the end of the study period, despite repeated attempts to obtain information. We also acknowledge the low uptake of hydroxyurea in our cohort (72/450 of HbSS/HbSβ^0 patients).

While life expectancy for a patient with SCD in the UK continues to improve, it still falls behind that in the general population in London, where it is 80.3 years for males, and 84.2 years for females.[11] We confirmed known predictors of mortality in SCD including markers of cardiorespiratory dysfunction, renal impairment and hemolysis as well as frequent hospitalization rate.[5,6,12-14] While these risk factors are not causative, they certainly contribute to the mortality and morbidity in SCD. These risk factors identify higher risk patients who perhaps should be prioritized for therapies including hydroxyurea and hematopoietic stem cell transplantation.

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Authorship contributions

KG and SLT designed the research study; KG, ED, and M Allman collected data; KG, ED, M. Allman, AM, M. Awogbade and SLT provided patient care and follow-up. KG and AD analysed the data; KG and SLT wrote the paper. All authors participated in editing the final version of paper.

Conflict of interest

The authors declare that they have no competing interests.

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Legends

Table 1A: Univariate Cox regression analysis for HbSS/HbSβ^0 thalassemia

Table 1B – Multivariate Cox regression analysis for HbSS/HbSβ^0 thalassemia

Figure 1: Kaplan Meier survival curves

1A) survival curve by sickle genotype

1B) survival curve for HbSS/Sβ^0, by hospitalization frequency

Table 1A – Univariate Cox regression analysis for HbSS/HbSβ^0 thalassemia

HbSS/HbSβ^0 thalassemia		**Hazard ratio (95% CI)**	**p value**
Demographics	α-thalassemia*	1.34 (0.67-2.71)	0.411
	Sex§	0.67 (0.34-1.34)	0.261
Admissions			
	High admission rate (>0.5/year) $^{\Phi}$	*3.13 (1.57-6.26)*	*0.001*
Hydroxycarbamide use		1.48 (0.57-3.86)	0.42
Transfusions		1.00 (0.35-2.87)	0.99
Steady state O_2 saturations	*Oxygen saturations <95%* $^{\infty}$	*2.84 (1.36-5.92)*	*0.005*
Hematology	*WBC x10^9/L*	*1.18 (1.04-1.35)*	*0.01*
	Hemoglobin g/L	0.98 (0.96-1.00)	0.07
	Platelets x10^9/L	1.00 (0.99-1.00)	0.16
	Reticulocytes x10^9/L	1.00 (1.00-1.00)	0.29
	Fetal hemoglobin high/low ‡	*0.44 (0.20-0.96)*	*0.04*
Biochemistry	*Lactate dehydrogenase IU/L*	*1.00 (1.00-1.00)*	*0.04*
	Ln C-reactive protein mg/L	*1.98 (1.16-3.38)*	*0.013*
	Ferritin >1000ug/L†	*2.52 (1.21-5.23)*	*0.013*
Liver enzymes	*Ln total bilirubin µmol/L*	1.78 (1.02-3.10)	0.04
	Ln aspartate transaminase IU/L	*3.84 (2.11-7.00)*	*<0.001*
	Ln alanine transaminase *IU/L*	2.37 (0.91-6.22)	0.08
	Ln γ-glutamyl transferase *IU/L*	1.44 (0.97-2.14)	0.07
	Ln alkaline phosphatase IU/L	*3.24 (1.93-5.45)*	*<0.0001*
Renal function	*Ln Creatinine µmol/L*	*2.11 (1.31-3.40)*	*0.002*
	Ln urinary albumin creatinine ratio mg/mmol	*1.34 (1.07-1.68)*	*0.01*

Significant hazards (risk factors) are *italicized*. Non-normal continuous variables were logged for statistical comparison. Dichotomous variables were handled as below:

* α-thalassemia, default=no
§ Sex, default=male
Φ Mean hospitalization rate, default ≤0.5admissions/year
∞ Oxygen saturations, default=normal (≥95%)
‡ HbF based on median split of validated HbF values, default HbF<5.5%
† Iron overload based on ferritin>1000ug/L, default=no

Table 1B – Multivariate Cox regression analysis for HbSS/HbSβ^0 thalassemia (age and sex as co-factors)

HbSS/HbSβ^0 thalassemia	**Hazard ratio (95% CI)**	**p value**
High admission rate (>0.5/year)	2.09 (1.02-4.29)	0.04
Ln Creatinine	3.13 (1.83-5.33)	<0.0001
Ln Aspartate transaminase	5.82 (2.93-11.54)	<0.0001

Figure 1A

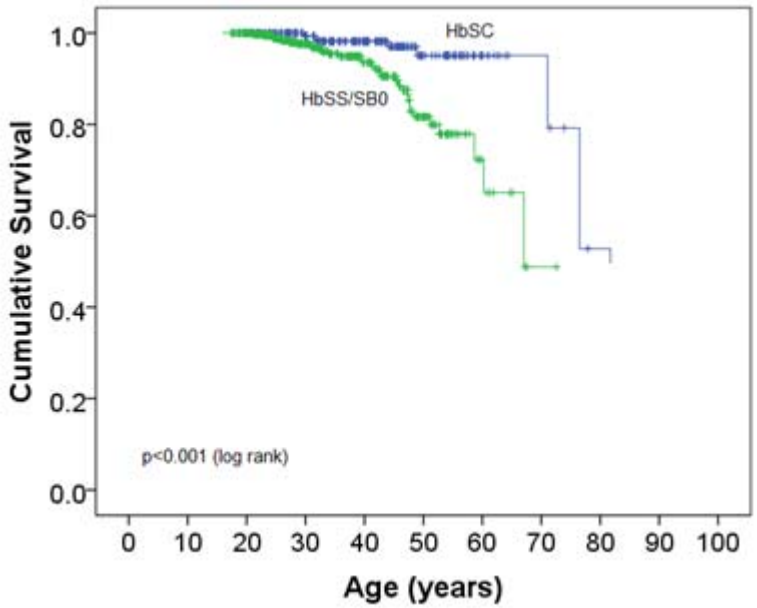

Figure 1B