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The association between tricuspid regurgitation velocity and 5-year survival in a North West London population of patients with sickle cell disease in the United Kingdom

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Summary

Raised tricuspid regurgitant velocity (TRV) occurs in approximately 30% of adults with sickle cell disease (SCD), and has been shown to be an independent risk factor for death. TRV was assessed in 164 SCD patients who were subsequently followed up for survival. Raised pulmonary pressures were defined as a TRV jet $\geq 2{\cdot}5$ m/s on echocardiography. Elevated TRV was present in 29·1% of patients and it was associated with increased age and left atrial diameter. There were 15 deaths (9·1%) over a median of 68·1 months follow up; seven patients had increased TRV, and eight patients had a TRV<2·5 m/s. Higher TRV values were associated with a greater than 4-fold increased risk of death (Hazard Ratio: 4·48, 99% confidence interval 1·01-19·8), although we found a lower overall mortality rate than has been reported in previous studies. TRV was not an independent risk factor for death. We have confirmed the association between raised TRV and mortality in a UK SCD population whose disease severity appears to be less than that reported in previous studies. Further prospective studies are needed to more clearly characterize which patient factors modify survival in SCD patients with raised TRV.

Keywords: sickle cell disease, pulmonary hypertension, mortality, survival, tricuspid regurgitation velocity.

Sickle cell disease (SCD) is one of the most prevalent genetic disorders worldwide, affecting approximately 12 000 people in the United Kingdom (Hickman *et al*, 1999; Lucas *et al*, 2008; Fitzhugh *et al*, 2010). Although life expectancy is reduced in SCD (Platt *et al*, 1994; Schultz & Ware, 2003), advances in management has led to a significant improvement in survival (Telfer *et al*, 2007; Quinn *et al*, 2010).

The development of pulmonary arterial hypertension (PAH) in SCD heralds a severe clinical phenotype, and is associated with death (Gladwin *et al*, 2004; Fitzhugh *et al*, 2010). Autopsy studies suggest that 75% of patients with SCD have histological findings of PAH at the time of death (Odd *et al*, 2009), suggesting that PAH may be clinically silent or poorly recognized. A raised tricuspid regurgitant velocity (TRV) on echocardiography is predictive of a raised systolic pulmonary arterial pressure (Hatle *et al*, 1981; Lanzarini *et al*, 2002), although this has a high negative predictive rate and cardiac catheterization is required to confirm the diagnosis of pulmonary hypertension (Parent *et al*, 2011; Fonseca *et al*, 2012). The ability to highlight a subgroup of patients with a high predicted mortality by use of a non-invasive measurement, such as TRV, represents a significant

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clinical advance and has rightly generated a lot of research interest. Raised TRV, as assessed by Doppler echocardiography, whether or not associated with PAH, is commonly found in SCD (Ataga *et al*, 2004) and has been reported as a marker of mortality in several major studies from the United States (Ataga *et al*, 2006; Anthi *et al*, 2007; De Castro *et al*, 2008; Machado & Gladwin, 2010; Lorch *et al*, 2011; Gladwin *et al*, 2012). Raised TRV has been found in 32–42% of patients with SCD (Gladwin *et al*, 2004; Akgul *et al*, 2007; Liem *et al*, 2007; Fitzhugh *et al*, 2010; Parent *et al*, 2011).

Studies in the UK using similar measurements and valuations have not been carried out, where differences in organization of health services and socio-demographics may lead to different findings.

The purpose of this study was to determine the survival of a cohort of patients with SCD, attending two hospitals in North West London, based on their TRV and describe differences between those with elevated and normal TRV.

Materials and methods

Patient population

All patients with SCD who were referred to the echocardiography laboratory of Hammersmith Hospital or Central Middlesex Hospital, London from the Sickle Cell or Haematology Clinics between August 2004 and May 2012 were studied retrospectively. The clinical indication for requesting the echocardiogram was either a clinical decision by their haematologist to screen for raised TRV or follow-up of previously elevated TRV. Only patients in stable condition were included; patients who had a vaso-occlusive crisis within the preceding 2 weeks or an episode of acute chest syndrome within 4 weeks were excluded.

The local research ethics committee issued a consent waiver to allow the review of the medical records. The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

Laboratory and clinical data

Laboratory data used for analysis were those recorded at the date closest to that of the echocardiogram. Only steady state results were included. The cause of death, when known, was obtained from the death certificate, medical records or general practitioner of the patient.

Transthoracic echocardiography

All studies were performed by an experienced sonographer using the Philips Sonos 7500, equipped with a transducer S3 1·8–3 MHz.

An electrocardiogram was simultaneously recorded from all subjects. Images were recorded and stored in digital format for subsequent off-line review and frame-by-frame analysis with ProSolv CardioVascular Analyser 3.5 (FUJIFILM Medical Systems USA Inc., Stamford, CT, USA). Two-dimensional echocardiographic examination and colour Doppler data were collected according to the recommendations of the American Society of Echocardiography (Gottdiener *et al*, 2004; Lang *et al*, 2005) using a standardized protocol.

Paraesternal long axis, short axis, right ventricular inflow, apical four, three and two chamber views were obtained. Transvalvular flow, Doppler determinations of the severity of the valvular regurgitation and left ventricular (LV) diastolic function were assessed.

Tricuspid regurgitation velocity was assessed in a minimum of four views and five sequential complexes were recorded. Continuous-wave Doppler of the peak regurgitant jet velocity was used to estimate the right-ventricular systolic pressure gradient using the modified Bernoulli equation [4 × (TRV)]. Pulmonary arterial systolic pressure (PASP) was estimated by adding the estimated mean right atrial (RA) pressure. The mean RA pressure was calculated according to the degree of collapse of the inferior vena cava with inspiration (Lang *et al*, 2005).

LV diastolic dysfunction was assessed using conventional echocardiographic parameters: mitral inflow peak early (E) and peak late (A) flow velocities, the E/A ratio, the deceleration time of early mitral flow velocity (DT), and the isovolumic relaxation time (IVRT) at rest and during the Valsalva manoeuvre. LV diastolic dysfunction was characterized by either normal (E/A ratio 0·9–1·5, DT 160–240 ms, IVRT 70–90 ms), restrictive (E/A ratio >2, DT <160 ms, IVRT <70 ms), or delayed relaxation (E/A ratio <0·9, DT >240 ms, IVRT >90 ms) (Quinones *et al*, 2002; Lester *et al*, 2008). Left atrial (LA) diameter was obtained from the paraesternal long axis view at the end-ventricular systole when the LA chamber was at its greatest dimension. RA volume was calculated by 2D-mode apical 4-chamber view using the area – length method. (Quinones *et al*, 2002; Lang *et al*, 2005).

Statistical analysis

Statistical analysis was performed using the Stata software (version 9.2, StataCorp, College Station, TX, USA).

Normally distributed variables were compared between groups using an unpaired *t*-test, while variables which lacked a normal distribution were compared using a Mann–Whitney test.

Distributions of continuous variables were shown by the mean ± standard deviation (SD) for normally distributed data or median and interquartile range for skewed data. Demographic, clinical and echocardiographic findings were compared according to TRV <2·5 vs. TRV ≥2·5 m/s by the Student's *t*-test for normally distributed continuous variables or the Kruskal–Wallis test for skewed continuous variables.

The relationship between two qualitative variables was analysed using the two-sided Fisher's exact test. The association between variables and TRV was examined using linear regression.

Patient survival was illustrated graphically using a Kaplan–Meier plot. Additionally, the effect of clinical and laboratory

variables on patient survival was examined using Cox regression analysis. Subsequently the joint effect of the explanatory variables upon survival was examined in a multivariate analysis. This multivariate analysis was restricted to those variables which showed some evidence of a significant effect from the univariate analyses ($P < 0{\cdot}1$). A backwards selection procedure was used to retain only those variables that were statistically significant. Before performing the multivariate analyses, the colinearity between variables was examined using variance inflation factors.

Due to large number of factors analysed, *P*-values of less than 0·01 were considered significant for the univariate analyses. A higher significance level of 0·05 was used for the multivariate analyses, so as not to omit potentially important predictors from the final model.

Results

Clinical characteristics of study population

A total of 170 adults with SCD were referred to the echocardiography laboratory and evaluated at Hammersmith and Central Middlesex hospital between August 2004 and May 2012. Echocardiogram and laboratory data were complete in 164 cases. Echocardiographic measurements of LV diastolic dysfunction were complete in 145 patients.

The median age of the 164 patients was 42·3 years (range 15–82 years), 114 were female (70%) and the median PASP was 28·0 mmHg [interquartile range (IQR) 22·9–32·6] One hundred and two patients had HbSS (62·2%), 41 HbSC (25%), 8 HbS-β^0 thalassaemia 4·9%), 11 HbS-β^+ thalassaemia (6·7%), and two had other genotypes, S-D Punjab and S/HPFH, (1·2%). The median follow-up interval was 68·1 months (IQR 48, 78) (Table Ia).

Elevated TRV was present in 29·1% of patients ($n = 48$): 12·8% had TRV $\geq$2·5–2·69 m/s, 10% had TRV 2·7–2·99 m/s and 6·1% had TRV $\geq$3·0 m/s. LV dilatation was seen in eight patients (5%) and reduced LV systolic function (ejection fraction <55%) in two patients. Twenty-six patients (16%) were on hydroxycarbamide therapy, of whom 19 had a TRV <2·5 m/s and seven patients had a TRV $\geq$2·5 m/s ($P = 0{\cdot}814$).

Five patients (3%) out of the 145 patients had echocardiographic evidence of LV diastolic dysfunction.

Associations with tricuspid regurgitation velocity

Results of the univariate analyses show that age, LA diameter and RA volume were significantly associated with TRV and a trend for an association with haemoglobin, ferritin and creatine levels (Table Ib).

Multivariate analysis indicated that both age and LA diameter were significantly associated with TRV (Table II). An increase in both of these two variables was associated with an increase in TRV. A 10-year increase in age was associated with a 0·06 unit (m/s) increase in TRV, while a

Table I. (a) Clinical characteristics of SCD patients. (b) Clinical associations with tricuspid regurgitation velocity in a univariate analysis of all patients.

		SCD patients
Clinical characteristics	*N*	Mean (SD)/ Median (IQR)*
Age (years)	164	42·3 (33, 50)*
Sex (male/female) (%)	164	(30/70)
Systolic blood pressure (mmHg)	136	120 (113, 129)*
Diastolic blood pressure (mmHg)	136	71·7 (11·6)
Body mass index (kg/m^2)	125	24 (22)*
Hydroxycarbamide therapy (%)	162	16
White blood cell count ($\times 10^9$/l)	157	9·1 (7·4, 10·9)*
Haemoglobin (g/l)	155	94 (80, 110)*
Ferritin (μg/l)	116	173 (83, 474)
Haematocrit (ratio)	150	0·27 (0·24, 0·32)*
Red blood cell count ($\times 10^{12}$/l)	153	3·32 (0·97)
Mean corpuscular volume (fl)	154	86·15 (79, 92)*
Creatinine (μmol/l)	156	70 (59, 85)*
Lactate dehydrogenase (iu/l)	102	606 (385, 879)*
Bilirubin (μmol/l)	149	35 (20–52)*
Tricuspid regurgitant velocity (m/s)	164	2·28 (0·42)
Pulmonary artery systolic pressure (mmHg)	164	28·04 (24, 33)*

Variable	Category	Coefficient (99% confidence interval)	*P*-value
Age†		0·10 (0·03, 0·16)	<0·001
Systolic blood pressure†		0·03 (−0·03, 0·10)	0·18
Genotype	HbSS/ HbS-β^0	0	
	Other genotypes	−0·09 (−0·28, 0·10)	0·23
Interventricular septum		0·04 (−0·02, 0·10)	0·09
Left ventricular posterior wall		0·02 (−0·03, 0·08)	0·26
Mitral valve E/A		−0·08 (−0·30, 0·13)	0·30
Mitral valve decelaration time‡		0·06 (−0·04, 0·16)	0·10
Left atrium diameter†		0·22 (0·08, 0·36)	<0·001
Right atrium volume†		0·09 (0·01, 0·17)	0·006
Body mass index§		−0·03 (−0·13, 0·07)	0·42
White blood cell count§		−0·02 (−0·16, 0·13)	0·73
Haemoglobin		−0·03 (−0·07, 0·01)	0·06
Fetal haemoglobin		−0·02 (−0·07, 0·03)	0·30
Platelet count‡		−0·01 (−0·05, 0·02)	0·26
Ferritin¶		0·16 (−0·05, 0·38)	0·05
Creatinine¶		0·48 (−0·02, 0·98)	0·01

SD, standard deviation.
*Median, IQR: interquartile range.
†Coefficients given for a 10 unit increase in explanatory variable.
‡Coefficients given for a 50 unit increase in explanatory variable.
§Coefficients given for a 5 unit increase in explanatory variable.
¶Variable analysed on the log scale (to base 10).

Table II. Clinical associations with tricuspid regurgitant velocity in a multivariate analysis of all patients.

Variable	Coefficient (95% confidence interval)	*P*-value
Age*	0·06 (0·01, 0·11)	0·02
Left atrium diameter*	0·18 (0·07, 0·29)	0·001

*Coefficients given for a 10 unit increase in explanatory variable. Variables entered into the analysis were age, left atria diameter, right atria volume, haemoglobin, ferritin and creatinine.

10-mm increase in LA diameter was associated with TRV values increasing by 0·18.

Patients in the study were further categorized according to TRV <2·5 vs. TRV ≥2·5 m/s. The results suggested that there was some evidence of a difference in SCD genotype between groups. HbSS or HbS-β^0 thalassaemia genotype was more common (80%) in patients with a TRV ≥2·5 when compared to a TRV <2·5 (64%), although the result was of borderline statistical significance ($P = 0·05$). Age, LV end-diastolic diameter (LVEDD), LA diameter, RA volume, haemoglobin and haematocrit were all found to vary significantly between the two groups (TRV <2·5 vs. TRV ≥2·5 m/s or more) (Table III). The LV ejection fraction was within normal limits in both groups. There were no differences in lung function tests between the two TRV groups.

Survival analysis

There were 15 deaths during follow-up (9·1%). Seven of these patients had increased TRV, giving a mortality of 16·67% (8 out of 48) in the high TRV group after 68 months median of follow-up time (range 4·0–84·3 months) compared to 6·9% in the lower TRV group (8 out of 116). In addition, A Kaplan–Meier analysis of the 5-year survival rates was 95·0% [95% confidence interval (CI), 89·7–97·6%].

The causes of death of patients with and without raised TRV are shown in Table IV. One patient with an unknown cause of death did not have an elevated TRV.

The effect of each variable upon survival was examined separately. When TRV was considered a continuous variable, there was a statistically significant association with survival ($P = 0·009$). Higher values of TRV were associated with an increased risk of death (HR: 4·48, 99% CI 1·01–19·8). A one-unit (1 m/s) increase in TRV was associated with the risk of death at any time increasing by more than 4-fold.

When TRV was considered as a categorical variable (TRV <2·5 m/s and TRV ≥2·5 m/s) as reported in previous studies (Gladwin *et al*, 2004; Parent *et al*, 2011; Fonseca *et al*, 2012), there was a trend to reduced survival in the group with raised TRV ($P = 0·06$), conforming with the association of TRV with an increased risk of death when assessed as a continuous variable (Fig 1).

Higher values of Hb, haematocrit and red blood cells were all associated with a decreased risk of death at any time in the univariate analysis. A 0·1 unit increase in haematocrit was associated with the hazard of death being only 20% as large (Table V).

The results of the multivariate analysis indicated that decreased Hb, increased mean corpuscular volume (MCV) and increased mitral valve (MV) DT were all still significantly associated with reduced patient survival (Table VI). The effects of

Table III. Clinical characteristics of all SCD patients without and with raised TRV.

Variable	TRV <2·5 m/s *n* = 116; Mean (SD)	TRV ≥2·5 m/s *n* = 48; Mean (SD)	*P*-value
Age (years)	41 (12)	46 (13)	0·04
Systolic blood pressure (mmHg)	121 (14)	123 (15)	0·40
Diastolic blood pressure (mmHg)	72 (12)	72 (11)	0·76
Interventricular septum (mm)	8·6 (1·5)	9·0 (1·3)	0·10
Left ventricular posterior wall (mm)	9 (8, 10)*	9 (8, 10)*	0·21
Left ventricular end-diastolic diameter (mm)	49 (5)	51 (6)	0·02
Left ventricular ejection fraction (%)	72 (7)	73 (6)	0·22
Mitral valve E/A	1·49 (0·35)	1·41 (0·56)	0·26
Mitral valve deceleration time (ms)	180 (160, 200)*	200 (162, 210)*	0·06
Left atrium diameter (mm)	37·2 (5·9)	40·7 (6·2)	0·001
Right atrial volume (cm^3)	53 (16)	69 (21)	0·003
Body mass index (kg/m^2)	25 (5)	24 (6)	0·20
Haemoglobin (g/l)	99 (20)	91 (21)	0·04
Haematocrit (ratio)	0·29 (0·06)	0·26 (0·07)	0·05
Red blood cell count ($\times 10^{12}$/l)	3·4 (0·9)	3·1 (1·1)	0·06
Automated absolute reticulocyte count ($\times 10^9$/l)	214 (96)	216 (100)	0·91
White blood cell count ($\times 10^9$/l)	9·1 (7·7, 10·8)*	9·3 (7·3, 11·6)*	0·80
Fetal haemoglobin (%)	4·2 (2·6, 8·6)*	3·5 (1·5, 6·0)*	0·41
Platelet count ($\times 10^9$/l)	317 (213, 393)*	301 (203, 390)*	0·73
Ferritin (μg/l)	155 (85, 395)*	267 (63, 692)*	0·19
Lactate dehydrogenase (iu/l)	562 (355, 816)*	784 (500, 993)*	0·06
Bilirubin (μmol/l)	34 (19, 48)*	44 (23, 62)*	0·08
Creatinine (μmol/l)	70 (58, 83)*	70 (61, 91)*	0·23
Hydroxycarbamide (%)	15·5	17·5	0·81
Number of admissions	0 (0, 1)*	0 (0, 2)*	0·38
Follow-up duration (months)	72·5 (47–79)	49·5 (33·7–76·7)	0·11†

SD, standard deviation; TRV, tricuspid regurgitant velocity.
*Median (Interquartile range).
†Deceased cases not considered.

Table IV. Cause of death and clinical characteristics in patients with SCD.

Patient	Gender	Age (years)	Follow-up time (months)	Phenotype	TRV (m/s)	Cause of death
1	F	42	68	HbSS	1·8	Respiratory failure
2	F	40	53	HbSS	1·9	Sudden death from sickle cell disease
3	F	35	80	HbSS	2·0	Intracerebral haemorrhage
4	M	58	74	HbSS	2·1	Liver failure (secondary to iron overload)
5	F	54	38	S-HPFH	2·1	Renal failure
6	0	75	71	HbSC	2·2	Post surgery complications
7	F	82	20	HbS-β^0	2·4	Unknown cause
8	M	49	70	HbSS	2·4	Cirrhosis liver failure
9	F	42	69	HbSS	2·7	Cardiomyopathy renal failure
10	F	49	43	HbSS	2·7	Hepatocellular cancer
11	0	25	20	HbSS	2·8	Road traffic accident
12	M	62	5	HbSS	3·0	Decompensated alcoholic liver disease; other problems: sepsis, haemolysis secondary to SCD
13	F	32	4	HbSS	3·1	Multiple organ failure, sepsis
14	F	68	70	HbSS	3·2	Cardiac failure
15	F	50	70	HbSS	3·4	Cardiac failure

TRV, tricuspid regurgitant velocity; SCD, sickle cell disease; F, female; M, male.

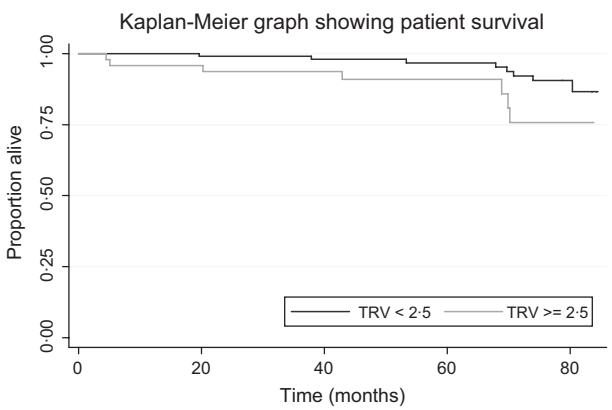

Fig 1. Kaplan–Meier Survival curves according to the tricuspid regurgitant velocity (TRV). The upper line is the survival estimate for sickle cell disease (SCD) patients without pulmonary hypertension (TRV <2·5 m/s). The lower line is the survival estimate for SCD patients with pulmonary hypertension (TRV $\geq$2·5 m/s). The number of patients at risk at the time of each death is shown for both groups. (P = 0·06).

TRV after adjusting for these three significant variables showed that there is no additional effect of TRV upon patient outcome. TRV was not found to be an independent risk factor for death.

Discussion

The major findings of this retrospective follow-up study of adults with SCD are a mortality of 16·67% in patients with a TRV $\geq$2·5 m/s after a median of 68 months follow-up, compared to a mortality of 6·9% in the lower TRV group, and the association between raised TRV and mortality with a greater than 4-fold increased risk of death when TRV was analysed as a continuous variable.

Although this association of increased mortality rate in patients with a raised TRV reflects previous studies from the US (Sutton *et al*, 1994; Gladwin *et al*, 2004), the overall mortality rates are much less marked in our study.

Three contemporary cohort studies in the US have reported a relationship between survival and raised TRV. Gladwin *et al* (2004) reported that a TRV of $\geq$2·5 m/s, as compared with a TRV <2·5 m/s, was independently associated with a marked increased risk of death (Relative Risk = 10·1; 95% CI = 2·2–47; P < 0·001). During 18·3 months mean follow-up the mortality was 16% for patients with a TRV of $\geq$2·5 m/s and was less than 2% in patients with a TRV <2·5 m/s. Follow-up data from this cohort continues to be updated and demonstrates that raised TRV remains a strong independent risk factor for death and carries a 40% mortality rate at 45 months. The estimated risk ratio of death for patients with TRV 2·5–3·0 m/s was 4·4 (95% CI = 1·6–12·2; P < 0·001) and for a TRV >3·0 m/s was 10·6 (95% CI = 3·3–33·6; P < 0·001). With regard to hydroxycarbamide use, 37% of the patients of the US cohort were on hydroxycarbamide therapy whilst in our cohort only 16% patients were on this treatment. In addition, we did not find an association with hydroxycarbamide use and mortality.

De Castro (2004) reported a similar prevalence of raised TRV (36% in patients with HbSS and HbS-β^0 thalassaemia and 25% in HbSC and HbS-β^+ thalassaemia and a similar 17% mortality rate at 24 months for patients with raised TRV after 2 years compared with approximately 2% mortality for patients without raised TRV. This last study used a different definition of raised TRV from other studies which was corrected for age, sex and body mass index, and the TRV was measured whilst the patient was hospitalized, not in steady state. Castro *et al* (2003) in a study with 34 adult patients, reported a 2-year mortality rate of 55% in patients

Table V. Proportional hazards (Cox) regression analysis of mortality.

Variable	Category	Hazard ratio (99% confidence interval)	*P*-value
Age*		1·48 (−0·92, 2·38)	0·03
Systolic blood pressure*		0·61 (0·31, 1·20)	0·06
Diastolic blood pressure*		0·54 (0·25, 1·18)	0·04
Genotype	HbSS/HbS-β^0 thalassaemia	1	
	Other genotypes	0·30 (0·04, 2·11)	0·11
Body mass index†		0·58 (0·28, 1·21)	0·06
Hydroxycarbamide (%)		1·35 (0·26, 7·22)	0·641
White blood cell count†		0·70 (0·20,2·42)	0·46
Haemoglobin		0·62 (0·404, 0·97)	0·006
Fetal haemoglobin		1·04 (0·86, 1·27)	0·59
Platelet count‡		0·95 (0·72, 1·26)	0·64
Ferritin§		2·77 (0·79, 9·80)	0·04
Creatinine		5·24 (0·18, 158)	0·21
Haematocrit¶		0·20 (0·05, 0·76)	0·002
Red blood cell count		0·33 (0·11, 0·93)	0·006
MCV*		1·59 (1·06, 2·41)	0·004
LDH‡		0·99 (0·89, 1·11)	0·91
Bilirubin§		1·02 (0·11, 9·56)	0·98
LVEDD*		1·24 (0·36, 4·17)	0·65
LVESD*		1·79 (0·43, 7·42)	0·29
Left atrium diameter*		2·24 (0·79, 46·35)	0·05
Right atrium volume*		0·81 (0·38, 1·71)	0·47
Mitral valve E/A		0·39 (0·06, 2·46)	0·19
Mitral valve DT‡		1·89 (1·23, 2·90)	<0·001
TRV (continuous)		4·48 (1·01, 19·8)	0·009
TRV	<2·5	1	
	≥2·5	2·71 (0·71, 10·4)	0·06

MCV, mean corpuscular volume; LDH, Lactate dehydrogenase; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; DT, deceleration time; TRV, tricuspid regurgitant velocity.

*Hazard ratios given for a 10 unit increase in explanatory variable.

†Hazard ratios given for a 5 unit increase in explanatory variable.

‡Hazard ratios given for a 50 unit increase in explanatory variable.

§Variable analysed on the log scale (to base 10).

¶Hazard ratios given for a 0·1 unit increase in explanatory variable.

Table VI. Multivariate analysis of mortality

Variable	Hazard ratio (95% confidence interval)	*P*-value*
Haemoglobin	0·58 (0·37, 0·93)	0·03
MCV†	1·89 (1·50, 2·77)	0·001
MV DT‡	2·69 (1·74, 4·17)	<0·001

MCV, mean corpuscular volume; MV DT, mitral valve deceleration time.

**P*-value used based on the Wald method.

†Hazard ratios given for a 10 unit increase in explanatory variable.

‡Hazard ratios given for a 50 unit increase in explanatory variable.

with a raised mean pulmonary artery pressure (MPAP; >25 mmHg) obtained by right heart catheterization, compared to a mortality rate of 21% in SCD without raised MPAP (≤25 mmHg).

Two older studies also reported increased mortality. Sutton *et al* (1994) found that a raised TRV was associated with a 40% mortality rate at 22 months in 60 patients, with an odds ratio for death of 7·86 (2·63–23·4). Powars *et al* (1988) found a mean survival of 2·5 years in patients with chronic lung disease and elevated TRV. Recently, a large multinational study (Gladwin *et al*, 2012) of unselected 632 screened patients, which used a more conservative cut-off value of TRV ≥3·0 m/s, showed that the association between TRV and mortality remained significant after adjustment for all other risk factors. In this study, 22 deaths were observed over median follow/up time of 29 months, of which 11 patients had TRV of at least 3·0 m/s. Current hydroxycarbamide use was not associated with mortality in this cohort.

In addition, we re-analysed the data using the conservative cut-off value of TRV ≥3 m/s and found no change in the results. Of the 164 patients included in our study, only 10 patients (6·1%) had a TRV value of 3·0 m/s or higher. Using the same time point as Gladwin *et al* (2012) (24 months) we found similar survival estimates of 99% for TRV <3·0 m/s and 80% for TRV ≥3·0 m/s. Nonetheless, using a time point of 68 months, there was no significant difference ($P = 0·125$) in the survival estimates: 95% for TRV <3·0 m/s and 80% for TRV ≥3·0 m/s. We also found that patients with higher TRV values had a higher risk of death (HR: 6·52; 95% CI 2·97–20·6; $P = 0·001$) when other factors are not considered (in comparison to a HR of 11·14 reported by Gladwin *et al*, 2012), however this risk disappears after adjustment for other variables associated with survival.

The lower mortality in our United Kingdom cohort raises the possibility that we studied a lower risk group of patients. On the other hand, our patients were selected randomly from those at higher risk attending out-patients clinics, whereas the patients studied by Gladwin *et al* (2012) were recruited from the community through multimedia advertisements, community outreach, and regional clinics, and it was not certain if these patients were receiving comprehensive care for SCD. In the study reported by Castro *et al* (2003) the selected patients were all hospitalized. This study preceded routine echo screening in the UK, so any selection bias is likely to have been positive rather than negative (i.e., patients who had symptoms of shortness of breath, or were thought to be at higher risk of pulmonary hypertension, or had a previous abnormal echocardiogram) were more likely to be referred for an echocardiogram, and this should have

increased, not decreased mortality rates. In addition, comparing our results to those of Gladwin *et al* (2012), our study had a significantly higher percentage of female patients and older patients, with a mean age of 42 years compared to 36 years and the latter should have biased the results in favour of increased mortality.

There was no significant difference in the sickle cell genotypes between the two studies (HbSS $P = 0{\cdot}45$; HbSC $P = 0{\cdot}7$; HbS β thalassaemia $P = 0{\cdot}68$) and no significant difference in the mean TRV ($P = 0{\cdot}15$). In both studies the overall number of deaths was small, which is reflected by the width of the confidence interval for TRV $\geq 2{\cdot}5$ m/s relative to TR <2·5 m/s. This means that the true hazard ratio in Gladwin *et al* (2012) could range from 2·2–47 ($P < 0{\cdot}001$), whereas in our study, the limits are from 0·71–10·4 although not significant ($P = 0{\cdot}06$), when TRV was categorized in the two groups (TR <2·5 and TRV $\geq 2{\cdot}5$ m/s). One explanation could be that the National Health Service (NHS) in the UK ensures that health care is free at the point of access and this may lead to patients with milder phenotypic disease being more likely to attend outpatient clinics and increase the numbers of patients with milder disease (and lower mortality) in the UK cohorts. On the other hand, easier NHS access to specialist sickle cell centres in the UK may result in better outcomes in terms of severity and overall quality of life. In addition, the mortality figures from the US data seem very high when compared with the UK experience. Although there are not sufficient longitudinal data for mortality of patients with SCD in the UK, the recent National Confidential Enquiry into Patient Outcome and Death report (Lucas *et al*, 2008), which collected data on all deaths in patients with haemoglobinopathies between January 2005 and December 2006, included only 81 reported deaths (including seven patients with thalassaemia), which in an estimated population of 12 000 for SCD in the UK, is a very low mortality rate. In essence, the reasons for this difference in mortality with United States cohorts is not explained by the clinical measurements which were made and further studies to confirm our findings are warranted.

In our study, the effect of TRV on outcome was dependent on markers of haemolysis, such as Hb and MCV. This is in contrast to the US studies which found raised TRV was an independent risk factor for death even after adjusting for causal factors such as those related to haemolysis. This and the greater overall mortality suggest a greater severity of SCD in these US patient cohorts. Why should this influence TRV as a marker of mortality? In the context of less severe SCD, end organ damage may be more directly related to haemolysis, whereas processes such as inflammation, endothelial hypertrophy and fibrosis may be more prominent in severe disease. These factors may in turn have influenced the relationship between haemolysis and survival.

In conclusion, we have confirmed the association between raised TRV and mortality in a UK SCD population attending two North West London specialist SCD centres, whose disease severity appears less than that reported in previous studies (Castro *et al*, 2003; Gladwin *et al*, 2004). Importantly, we did not find TRV as an independent risk factor for death. Nonetheless, of key importance to our study is the difference between mortality rates in this UK SCD population as compared to the US. Further prospective studies will enable us to more clearly characterize which patient factors modify survival in SCD patients with raised TRV.

Study limitations

In our study, a limited number of echocardiographic measurements were made at the time of these clinical studies and early studies did not include tissue Doppler. The assessment of RV function and dimensions was qualitative. The value of the MV E/A ratio in evaluating LV diastolic dysfunction may be limited and is dependent on intravascular volume status. Its results in SCD may be confounded by volume overload and may not accurately reflect the diastolic function of the left ventricle. As this is a retrospective study, the selection of patients was not controlled so selection bias may have arisen. However, this remains one of the largest cohorts published to date and, to the best of our knowledge, with the longest follow-up period reported.

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Authorship contributions

I.Z. Cabrita designed the research, wrote the manuscript, collected and analysed the data; A. Mohammed helped in the collection of data and writing of the manuscript, M. Layton designed the research, enrolled the patients and contributed to the critical revision of the manuscript; S. Ghorashian, designed the research, collected the data and contributed substantially to the critical revision and writing of the manuscript; A. Gilmore, collected the data and contributed to the critical revision and writing of the manuscript; G. Cho enrolled the patients and contributed to the critical revision of the manuscript; Jo Howard enrolled the patients and contributed significantly to the critical revision and writing of the manuscript; K.A. Anie contributed to the review and critical revision of the manuscript; L. Desforges and J. Grapsa helped in the acquisition and collection of data; Luke Howard contributed to the critical revision of the manuscript, G. Mahalingam contributed with the collection

of data; P. Bassett performed the statistical analysis; F.J. Pinto and P. Nihoyannopoulos contributed to the critical revision of the manuscript; S.C. Davies and J.S.R. Gibbs designed the research, contributed to the critical revision and writing of the manuscript and interpretation of the data.

Conflict of interest disclosures

No author has any financial or personal relationships with people or organizations that could inappropriately influence this work. The authors have no competing interests.

References

Akgul, F., Yalcin, F., Seyfeli, E., Ucar, E., Karazincir, S., Balci, A. & Gali, E. (2007) Pulmonary hypertension in sickle-cell disease: comorbidities and echocardiographic findings. *Acta Haematologica*, **118**, 53–60.

Anthi, A., Machado, R.F., Jison, M.L., Taveira-Dasilva, A.M., Rubin, L.J., Hunter, L., Hunter, C.J., Coles, W., Nichols, J., Avila, N.A., Sachdev, V., Chen, C.C. & Gladwin, M.T. (2007) Hemodynamic and functional assessment of patients with sickle cell disease and pulmonary hypertension. *American Journal of Respiratory and Critical Care Medicine*, **175**, 1272–1279.

Ataga, K.I., Sood, N., De Gent, G., Kelly, E., Henderson, A.G., Jones, S., Strayhorn, D., Lail, A., Lieff, S. & Orringer, E.P. (2004) Pulmonary hypertension in sickle cell disease. *The American Journal of Medicine*, **117**, 665–669.

Ataga, K.I., Moore, C.G., Jones, S., Olajide, O., Strayhorn, D., Hinderliter, A. & Orringer, E.P. (2006) Pulmonary hypertension in patients with sickle cell disease: a longitudinal study. *British Journal of Haematology*, **134**, 109–115.

Castro, O., Hoque, M. & Brown, B.D. (2003) Pulmonary hypertension in sickle cell disease: cardiac catheterization results and survival. *Blood*, **101**, 1257–1261.

De Castro, L. (2004) Pulmonary hypertension in SS, SC and S thalassemia: prevalence, associated clinical syndromes, and mortality. *Blood*, **104**, 462a.

De Castro, L.M., Jonassaint, J.C., Graham, F.L., Ashley-Koch, A. & Telen, M.J. (2008) Pulmonary hypertension associated with sickle cell disease: clinical and laboratory endpoints and disease outcomes. *American Journal of Hematology*, **83**, 19–25.

Fitzhugh, C.D., Lauder, N., Jonassaint, J.C., Telen, M.J., Zhao, X., Wright, E.C., Gilliam, F.R. & De Castro, L.M. (2010) Cardiopulmonary complications leading to premature deaths in adult patients with sickle cell disease. *American Journal of Hematology*, **85**, 36–40.

Fonseca, G.H., Souza, R., Salemi, V.M., Jardim, C.V. & Gualandro, S.F. (2012) Pulmonary hypertension diagnosed by right heart catheterisation in sickle cell disease. *European Respiratory Journal*, **39**, 112–118.

Gladwin, M.T., Sachdev, V., Jison, M.L., Shizukuda, Y., Plehn, J.F., Minter, K., Brown, B., Coles, W.A., Nichols, J.S., Ernst, I., Hunter, L.A., Blackwelder, W.C., Schechter, A.N., Rodgers, G.P., Castro, O. & Ognibene, F.P. (2004) Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. *The New England Journal of Medicine*, **350**, 886–895.

Gladwin, M.T., Barst, R.J., Gibbs, J.S.R., Hildesheim, M., Sachdev, V., Nouraie, M., Hassell, K.L., Little, J.A., Schraufnagel, D.E., Krishnamurti, L., Novelli, E.M., Girgis, R.E., Zhang, Y., Morris, C.R., Rosenzweig, E.B., Badesch, D.B., Lanzkron, S., Castro, O.L., Taylor, J.G., Goldsmith, J.C., Gordeuk, V.R., Kato, G.J. & Machado, R. (2012) Risk factors for death in 632 patients with sickle cell Anemia in the United States and United Kingdom. *Blood* (ASH Annual Meeting Abstracts), **120**, 3240.

Gottdiener, J.S., Bednarz, J., Devereux, R., Gardin, J., Klein, A., Manning, W.J., Morehead, A., Kitzman, D., Oh, J., Quinones, M., Schiller, N.B., Stein, J.H. & Weissman, N.J. (2004) American Society of Echocardiography recommendations for use of echocardiography in clinical trials. *Journal of the American Society of Echocardiography*, **17**, 1086–1119.

Hatle, L., Angelsen, B.A. & Tromsdal, A. (1981) Non-invasive estimation of pulmonary artery systolic pressure with Doppler ultrasound. *British Heart Journal*, **45**, 157–165.

Hickman, M., Modell, B., Greengross, P., Chapman, C., Layton, M., Falconer, S. & Davies, S.C. (1999) Mapping the prevalence of sickle cell and beta thalassaemia in England: estimating and validating ethnic-specific rates. *British Journal of Haematology*, **104**, 860–867.

Lang, R.M., Bierig, M., Devereux, R.B., Flachskampf, F.A., Foster, E., Pellikka, P.A., Picard, M.H., Roman, M.J., Seward, J., Shanewise, J.S., Solomon, S.D., Spencer, K.T., Sutton, M.S. & Stewart, W.J. (2005) Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *Journal of the American Society of Echocardiography*, **18**, 1440–1463.

Lanzarini, L., Fontana, A., Lucca, E., Campana, C. & Klersy, C. (2002) Noninvasive estimation of both systolic and diastolic pulmonary artery pressure from Doppler analysis of tricuspid regurgitant velocity spectrum in patients with chronic heart failure. *American Heart Journal*, **144**, 1087–1094.

Lester, S.J., Tajik, A.J., Nishimura, R.A., Oh, J.K., Khandheria, B.K. & Seward, J.B. (2008) Unlocking the mysteries of diastolic function: deciphering the Rosetta Stone 10 years later. *Journal of the American College of Cardiology*, **51**, 679–689.

Liem, R.I., Young, L.T. & Thompson, A.A. (2007) Tricuspid regurgitant jet velocity is associated with hemolysis in children and young adults with sickle cell disease evaluated for pulmonary hypertension. *Haematologica*, **92**, 1549–1552.

Lorch, D., Spevack, D. & Little, J. (2011) An elevated estimated pulmonary arterial systolic pressure, whenever measured, is associated with excess mortality in adults with sickle cell disease. *Acta Haematologica*, **125**, 225–229.

Lucas, S.B., Mason, D.G., Mason, M. & Weyman, D. on behalf of NCEPOD. (2008) *A sickle crisis? A report for the national confidential enquiry into patient outcome and death (NCEPOD)*. NCEPOD, London, UK.

Machado, R.F. & Gladwin, M.T. (2010) Pulmonary hypertension in hemolytic disorders: pulmonary vascular disease: the global perspective. *Chest*, **137**(Suppl. 6), 30S–38S.

Odd, B.-H., Nedim, S., Bengt, R. & Jonas, W. (2009) Doppler echocardiography can provide a comprehensive assessment of right ventricular afterload. *Journal of the American Society of Echocardiography*, **22**, 1360–1367.

Parent, F., Bachir, D., Inamo, J., Lionnet, F., Driss, F., Loko, G., Habibi, A., Bennani, S., Savale, L., Adnot, S., Maitre, B., Yaici, A., Hajji, L., O'Callaghan, D.S., Clerson, P,.Girot, R., Galacteros, F. & Simonneau, G. (2011) A hemodynamic study of pulmonary hypertension in sickle cell disease. *The New England Journal of Medicine*, **365**, 44–53.

Platt, O.S., Brambilla, D.J., Rosse, W.F., Milner, P.F., Castro, O., Steinberg, M.H. & Klug, P.P. (1994) Mortality in sickle cell disease – life expectancy and risk factors for early death. *The New England Journal of Medicine*, **330**, 1639–1644.

Powars, D., Weidman, J.A., Odom-Maryon, T., Niland, J.C. & Johnson, C. (1988) Sickle cell chronic lung disease: prior morbidity and the risk of pulmonary failure. *Medicine* (Baltimore), **67**, 66–76.

Quinn, C.T., Rogers, Z.R., McCavit, T.L. & Buchanan, G.R. (2010) Improved survival of children and adolescents with sickle cell disease. *Blood*, **115**, 3447–3452.

Quinones, M.A., Otto, C.M., Stoddard, M., Waggoner, A. & Zoghbi, W.A. (2002) Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American

Society of Echocardiography. *Journal of the American Society of Echocardiography*, **15**, 167–184.

Schultz, W.H. & Ware, R. (2003) Malignancy in patients with sickle cell disease. *American Journal of Hematology*, **74**, 249–253.

Sutton, L.L., Castro, O., Cross, D.J., Spencer, J.E. & Lewis, J.F. (1994) Pulmonary hypertension in sickle cell disease. *American Journal of Cardiology*, **74**, 626–628.

Telfer, P., Coen, P., Chakravorty, S., Wilkey, O., Evans, J., Newell, H., Smalling, B., Amos, R., Stephens, A., Rogers, D. & Kirkham, F. (2007) Clinical outcomes in children with sickle cell disease living in England: a neonatal cohort in East London. *Haematologica*, **92**, 905–912.