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ORIGINAL ARTICLE

East Mediterranean region sickle cell disease mortality trial: retrospective multicenter cohort analysis of 735 patients

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Abstract Sickle cell disease (SCD), one of the most common genetic disorders worldwide, is characterized by hemolytic anemia and tissue damage from the rigid red blood cells. Although hydroxyurea and transfusion therapy are administered to treat the accompanying tissue injury, whether either one prolongs the lifespan of patients with SCD is unknown. SCD-related mortality data are available, but there are few studies on mortality-related factors based on evaluations of surviving patients. In addition, ethnic variability in patient registries has complicated detailed analyses. The aim of this study was to investigate mortality and mortality-related factors among an ethnically homogeneous population of patients with SCD. The 735 patients (102 children and 633 adults) included in this retrospective cohort study were of Eti-Turk origin and selected from 1367 patients seen at 5 regional hospitals. A central population management system was used to control for records of patient mortality. Data reliability was checked by a data supervision group. Mortality-related factors and predictors were identified in univariate and multivariate analyses using a Cox regression model with stepwise forward selection. The study group included patients with homozygous hemoglobin S (Hgb S) disease (67 %), Hb S-β^0 thalassemia (17 %), Hgb S-β^+ thalassemia (15 %), and Hb S-α thalassemia (1 %). They were followed for a median of 66 ± 44 (3–148) months. Overall mortality at 5 years was 6.1 %. Of the 45 patients who died, 44 (6 %) were adults and 1 (0.1 %) was a child. The mean age at death was 34.1 ± 10 (18–54) years for males, 40.1 ± 15 (17–64) years for females, and 36.6 ± 13 (17–64) years overall. Hydroxyurea was found to have a notable positive effect on mortality ($p = 0.009$). Mortality was also significantly related to hypertension and renal damage in a univariate analysis ($p = 0.015$ and $p = 0.000$, respectively). Acute chest syndrome, splenic sequestration, and prolonged painful-crisis-related multiorgan failure were the most common causes of mortality. In a multivariate analysis of laboratory values, only an elevated white blood cell count was related to mortality ($p = 0.009$). These data show that despite recent progress in the treatment of SCD, disease-related factors continue to result in mortality in young adult patients. Our results highlight the importance of evaluating curative treatment options for patients who have an appropriate stem cell donor in addition to improving patient care and patient education.

Keywords Sickle cell disease · Mortality · Painful crisis · Acute chest syndrome · Hemoglobinopathy

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Introduction

Sickle cell disease (SCD) is characterized by chronic hemolysis, anemia, typical painful crises, and tissue and organ damage. It is one of the most common genetic disorders worldwide, with an estimated 312,000 neonates homozygous for mutant hemoglobin (Hgb) S worldwide [1]. The Hgb S trait occurs in 13.6 % of the population living in the Mediterranean region of Turkey [2]. The clinical course of SCD widely varies. Differences in the clinical symptoms among patients with organ damage have been attributed to genetic factors besides Hgb S [3]. Consequently, there is a need to evaluate SCD from a multigenetic perspective despite the fact that it is a single-gene disease [4]. SCD is a progressive and life-threatening disease which can lead to irreversible organ damage and resulting in a markedly reduced life expectancy [5, 6]. The mean lifespan of patients with SCD in the USA is only 39 years, and the risk of death is higher in adults than in children [7]. SCD-related mortality is expected to vary among communities depending on the genetic features of the respective populations and the quality of medical care. Previous mortality studies mostly investigated the causes of death and age at death from SCD and the mortality ratios across decades [8, 9], whereas few studies have investigated the factors influencing mortality based on comparisons of dying and surviving patients. In these studies, hydroxyurea effect on mortality is not clear particularly in adult patients [10]. However, such studies may lead to improvements in the treatment and medical care services offered to patients with SCD and in decision-making regarding curative treatment options such as stem cell transplantation.

In this study, data on mortality and the factors affecting mortality were investigated by comparing patients with SCD who have survived with those who died of the disease. The patient population was ethnically homogenous and mostly from the East Mediterranean region of Turkey.

Method

Patients and study plan

This study was planned as a multicenter, cross-sectional, retrospective cohort study. Pediatric and adult patients living in three cities in the East Mediterranean region of Turkey and followed up in the Hematology Departments of five regional hospitals from 2005 to 2015 were included in the study. All patients were of Eti-Turk origin and had been diagnosed with homozygous Hgb S or heterozygous combinations of Hgb S and thalassemia (Hgb S-β thalassemia, Hgb S-α thalassemia) by hemoglobin electrophoresis, or genetic analysis who were regularly followed in clinic at the hospitals [11–13]. Patient records were accessed from the data management systems of the hospitals, from patient files, and from a central population management system. Data on the age at death and the cause of death were investigated together with clinical and laboratory data influencing mortality.

The primary endpoint was the crude mortality rate of the SCD population and patient age at death. The secondary endpoint comprised mortality-related factors and predictors. Patients not definitively diagnosed with SCD but who were diagnosed with a malignancy, died of malignancy or trauma, or had undergone bone marrow transplantation were excluded from the study. Patient records that did not include data on at least half of the endpoints were considered insufficient and were not included in the study.

This study was approved by the Institutional Medical and Health Sciences Experimental/Clinical Research Principles and Research Committee (project number: KA15/07). The required approvals for the collaborations in the study were obtained from the concerned departments and hospitals.

Data collection and reliability

The clinical and laboratory data of the patients were obtained from the modular system created for patients with SCD in the Hospital Data Management System of Baskent University (Nucleus, version 9.3.39; Monad Software Company, Ankara). Data on the participants from the other institutions were obtained from the respective Hospital Data Management Systems and patient files. The Ministry of Health's Central Population Management System was used to confirm mortality records. Age at death and cause of death were recorded for the patients who died.

Clinical data included patient age, diagnosis, treatment with hydroxyurea, number of painful crises per year, smoking, family history, transfusion requirement, history of red cell exchange, acute chest syndrome, hypertension, renal damage, heart failure, pulmonary hypertension, pulmonary thromboembolism, deep venous thrombosis, and cerebrovascular events. Laboratory data included the steady-state Hgb level, leukocyte and platelet counts, and the ratio of abnormal Hgb (Hgb S, Hgb F, Hgb A2) to total Hgb.

The data were checked by the Data Supervision Group of Baskent University Hospital and by the responsible hematologist in the clinics of the other participating institutions.

Definitions

Patients who had not required medication to treat painful conditions for the previous 4 weeks were considered to have steady-state disease. A painful crisis was defined as the need for hospital admission due to pain not related to any cause other than SCD or for the use of parenteral nonsteroidal anti-inflammatory inhibitors, metamizol, and narcotics for SCD-related pain treatment [11, 13]. The crisis frequency was

defined as rare if the patient experienced fewer than three painful crises a year, and frequent if the number of yearly painful crises was three or more. This classification was based on the SCD high-risk group criteria of the bone marrow transplantation list of the Social Security Institution of Turkey [14]. Microalbuminuria was defined as 30 to 300 mg of microalbumin per day in a spot urine test in an afebrile patient with episodes of pain. Nephropathy was defined as the presence of at least one indicator of renal dysfunction, such as microalbuminuria and proteinuria, hyperechogenicity and/or thinning of the renal cortex on ultrasonography, and low creatinine clearance. Pulmonary hypertension was defined as a mean resting pulmonary artery pressure of >25 or >30 mmHg following exercise and a pulmonary capillary pressure of <15 mmHg. The pulmonary artery systolic pressure was defined as right ventricle outlet stenosis and tricuspid regurgitation in patients who did not have pulmonary artery stenosis as determined on echocardiography [15].

Hydroxyurea use was defined as the regular use of 15 mg hydroxyurea/kg/day for at least 1 month. Transfusion therapy was defined as having received a transfusion six times or more per year or participation in a red cell exchange program or having received one or more red cell exchanges per year.

Statistics

Statistical analysis was done using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Categorical measurements are expressed as the number and percent, and continuous variables as the mean ± standard deviation or median and minimum–maximum, when required. Categorical variables were compared using the χ^2 test or Fisher's exact test. Distributions were controlled in comparisons of mortality and continuous measurements; Student's *t* test and the Mann–Whitney *U* test were used in analyses of parametric and nonparametric variables, respectively. Mortality-related factors and predictors were identified by univariate and multivariate analyses using a Cox regression model with stepwise forward selection.

A p value of <0.05 was considered to indicate statistical significance.

Results

Patients and data on mortality

Based on the records of 1367 patients with SCD, 735 patients (368 females and 367 males) with sufficient clinical data were included in the study. The vast majority of the included patients had homozygous Hgb S disease. The study group comprised both adult (age ≥18 years; $n = 633$) and pediatric (age <18 years; $n = 102$) patients. The youngest patient was 3 years old, and the oldest patient was 67 years old. The mean age overall was 30.2 ± 11.2 years; in the adults, it was 32.9 ± 9.5 (19–67) years and in the pediatric patients 13.5 ± 4 (3–18) years. The clinical characteristics of the patients are shown in Table 1.

The patients were followed for a median of 66 ± 44 (3–148) months. Within the group as a whole, there were 689 survivors and 45 patients who died of various causes. Only one of the dying patients was under 18 years of age. Of the dying adult patients, 62.8 % were male and 37.2 % were female. The relationship between mortality and male sex among the adult patients who died was statistically significant ($p = 0.041$). The overall crude mortality rate of the patients was 6.1 % (6.0 % in adults, 0.1 % in children). The mean age at death was 36.6 ± 13 years, 34.1 ± 10 (18–54) years in males and 40.1 ± 15 (17–64) years in females.

An analysis of the patients according to mean age at death by decade showed that before 2009, these patients were male and had a mean age at death of 30.5 ± 13 (21–41) years. In the group of patients who died between 2010 and 2012, the mean age at death was 33.3 ± 11 (21–54) years for males and 38.3 ± 12 (31–52) for females. Among the patients who died after 2013, the mean age at death was 37.5 ± 10 (27–53) years for males and 38.0 ± 15 (17–64) years for females.

Mortality-related clinical factors

Cause of mortality could be defined in 28 out 45 patients; however, 17 were reported as unidentified as cause of mortality could not be obtained from patient records. The most common causes of death were acute chest syndrome followed by splenic sequestration and prolonged painful-crisis-related multiorgan failure.

The distribution of the causes of death is shown in Table 2.

When the patients were evaluated according to the number of painful crises per year, there was no statistically significant difference between dying and surviving patients with respect to the painful crisis frequency, either in adults or in pediatric patients. Hydroxyurea use was higher among adult patients who survived (62.3 %) than in those who later died (41.9 %) ($p = 0.009$). This difference was not statistically significant among pediatric patients ($p = 0.417$). Dying and surviving patients did not significantly differ in their smoking status.

Transfusion therapy is frequently used for patients with SCD. In our study, 484 (65.8 %) patients had been treated with blood transfusion therapy and 251 (34.2 %) did not. Among the patients who died, 73.3 % had received transfusion therapy compared with 65.4 % of the surviving patients. The relationship between mortality and transfusion therapy was not statistically significant. On the other hand, a total of 46 pregnancies were recorded in this study. Thirty-three patients had received a standard prophylactic red blood cell exchange therapy. The remaining 13 patients had received clinically indicated transfusion therapy. In red blood cell

Table 1 Clinical characteristics

Variable		Survival *n* (%)	Death *n* (%)
Age			
	<18 years	101 (15)	1 (2)
	≥19 years	578 (85)	44 (98)
Gender			
	Male	334 (49)	27 (60)
	Female	345 (51)	18 (40)
Frequency of painful crisis			
	<3/year	507 (75)	36 (80)
	≥3/year	172 (25)	9 (20)
Nephroropathy (microalbuminuria/proteinuria)			
	Present	113 (16.8)	21 (47)
	None	564 (83)	24 (53)
	Unknown	2 (0.2)	–
Use of hydroxyurea			
	Present	438 (65)	19 (42)
	None	241 (35)	26 (58)
Acute chest syndrome			
	Present	69 (10)	9 (20)
	None	610 (90)	20 (44.5)
	Unknown	–	16 (35.5)
Pulmoner hypertension			
	Present	212 (31)	15 (33)
	None	464 (68.5)	30 (67)
	Unknown	3 (0.5)	–
Cardiac failure			
	Present	18 (2.5)	4 (9)
	None	658 (97)	41 (91)
	Unknown	3 (0.5)	–
Hypertension			
	Present	26 (3.7)	6 (13)
	None	651 (95.8)	39 (87)
	Unknown	2 (0.5)	–
Cerebrovascular disorder			
	Present	64 (9.8)	6 (13)
	None	613 (90)	39 (87)
	Unknown	2 (0.2)	–
Deep venous thrombosis			
	Present	15 (2)	1 (2)
	None	661 (97.5)	43 (97.9)
	Unknown	3 (0.5)	1 (0.1)
Pulmonary thromboembolism			
	Present	14 (2)	3 (7)
	None	663 (97.8)	42 (43)
	Unknown	2 (0.2)	–
Smoking			
	Present	86 (13)	7 (16)
	None	593 (87)	38 (84)
Transfusion therapy			
	Present	441 (65)	33 (73)
	None	238 (35)	12 (27)
Total		679 (100)	45 (100)

exchange group, thirty-three patients (17.4 % of patients with SCD had a second gravida) had delivered by cesarean section with no maternal, perinatal or neonatal death. Four of the seven pregnant patients who do not receive standard prophylactic exchange protocol had died. There was a significant difference between groups in terms of maternal mortality ($p = 0.010$).

The results of the analysis of the relationship between SCD-related tissue damage and accompanying diseases and mortality in adults are shown in Table 3. Acute chest syndrome, hypertension, and renal disease were identified as significant risk factors in adults ($p = 0.007$, $p = 0.015$, and $p = 0.000$, respectively). Among the pediatric patients, there was only one death, which occurred in a patient with acute chest syndrome. Therefore, a comparison of surviving vs. dying pediatric patients with respect to mortality-related factors was not possible. One pediatric patient had pulmonary hypertension, whereas pulmonary embolism,

Table 2 Causes of death

Cause	Number	Percent
Acute chest syndrome	8	28.5
Splenic sequestration	4	14.2
Prolongation of painful crisis and multiorgan failure	3	10.7
Acute liver failure/DIC	3	10.7
Septic chock	2	7.0
Hemolytic crisis	2	7.0
Gastrointestinal bleeding	1	3.5
Cardiac failure	1	3.5
Pulmonary thromboembolism	1	3.5
Pneumonia	1	3.5
Lung edema	1	3.5
Pregnancy/pre-eclampsia/eclampsia	1	3.5
Unidentified	17	37.7
Total	45	100

deep venous thrombosis, renal damage, hypertension, and heart failure were not detected in any of the pediatric patients.

Mortality-related laboratory factors

In a univariate analysis, the hemoglobin level, leukocyte count, platelet number, and mortality were significantly associated with adult mortality ($p = 0.000$ for all). A multivariate analysis of these same parameters showed that only the relationship between elevated leukocyte counts and adult mortality was significant ($p = 0.009$) (Table 4). In pediatric patients, this relationship was not significant. Hemoglobin type was also not related to mortality. A Cox regression model extracted from Baskent data including 324 adult SCD patients revealed low hemoglobin, and elevated leukocyte counts were also associated with survival (Table 5).

Table 3 Comparison of complications between dying and surviving patients

	Dying % (*n*)	Surviving % (*n*)	*P* value
Renal damage	48.8 (21)	19.6 (113)	0.000
Pulmonary hypertension	34.9 (15)	36.6 (211)	0.938
Acute chest syndrome	20.9 (9)	7.6 (44)	0.007
Hypertension	14.0 (6)	4.3 (25)	0.015
Cerebrovascular disease	11.6 (5)	7.5 (43)	0.367
Heart failure	9.3 (4)	3.1 (18)	0.059
Pulmonary thromboembolism	7.0 (3)	2.4 (14)	0.107
Deep venous thrombosis	2.4 (1)	2.6 (15)	1.000

Table 4 Logistic regression analysis affecting mortality in patients with sickle cell disease

Variable	β	SE	Sig. (*p*)	OR	CI 95 %
Age	−0.048	0.042	0.259	0.953	0.878–1.036
Gender	1.935	1.129	0.086	6.926	0.758–63.270
Hydroxyurea use	0.770	0.866	0.374	2.160	0.396–11.779
Acute chest syndrome	1.438	0.961	0.135	4.212	0.640–27.713
Hypertension	1.100	1.253	0.380	3.005	0.258–35.016
Renal damage	1.049	0.995	0.292	2.855	0.406–20.063
Leukocyte count	0.062	0.024	0.009	1.064	1.016–1.114
Platelet value	−0.002	0.002	0.478	0.998	0.994–1.003
Hemoglobin value	−0.276	0.227	0.223	0.759	0.487–1.183

SE standard error, *OR* odds ratio, *CI* confidence interval

Discussion

SCD is a benign hematologic disease, but its clinical course and risks in many ways mimic those of a malignancy [7, 16]. Despite current knowledge of the pathogenesis of SCD and improved patient management, neither the quality of life nor the lifespan of patients with SCD has benefited accordingly. The discrepancy can in part be explained by the fact that both the variable clinical features of SCD and the tissue damage are related to genetic factors other than the known gene mutation in beta globin [17]. In addition, the quality of patient care varies and depends on the different populations, including their culture, the medical expertise that is available, and the institutional organization [5]. In our study of the causes of death in patients with SCD, these sources of heterogeneity were minimized by evaluating a population with close family relationship, the same ethnic origin, and a similar level of health care. By assessing the age at death and the factors that influence mortality, our study contributes to discussions on curative treatment options and their indications.

Unlike the previous studies, the significant findings in this study and their interpretations can be summarized as follows.

Age at death

According to the literature data, the average life expectancy of patients with SCD in the USA in the 1970s was <20 years. In another study, the life expectancy was 42 years for males and 48 years for females [16]. Lanzkron et al. [8] reported that patients with SCD in the USA in 2005 had a life expectancy of 38 years for males and 42 years for females. In a 2006 study conducted in the USA, the average lifespan was 39 years [18, 19]. Elmariah et al. [19] reported a younger mortality age for male SCD patients compared to females, consistently with the results of our study. This difference may be attributed to mortality-related factors which are more frequent in males such as atherosclerosis, pulmonary complications, and

Table 5 Cox regression model and hazard ratios for lab parameters extracted from Baskent data

Variable	B	SE	Wald	df	*P*-value	HR	95.0% CI	
							Lower	Upper
HgbA (%)	-.028	.124	.052	1	.819	.972	.763	1.239
Hgb S(%)	-.064	.126	.261	1	.609	.938	.733	1.200
Hgb A2 (%)	,036	.207	.031	1	.860	1.037	.692	1.554
Hgb F (%)	-.063	.124	.259	1	.611	.939	.737	1.196
Hgb (g/dL)	-.486	.155	9.772	1	.002	.615	.454	.834
WBC (× 109/L)	.099	.026	14.333	1	.000	1.104	1.049	1.163

Hgb hemoglobin, *WBC* white blood cell, *SE* standard error, *HR* hazard ratio, *CI* confidence interval

hormonal effects. However, sufficient data are not available in literature. We can also speculate that male patients are more prone to develop infections, since they spend more time outside their family environment.

Studies of SCD and ethnicity have shown that in the USA, among the patients with SCD alive at age 45 years, 35 % were from African-American and Hispanic cohorts [18]. In a Jamaican cohort, 50 % of the patients with SCD were still alive at the age of 55 years [20]. The mean age at death in our patients was lower, which can perhaps be attributed to the genetic features of this Mediterranean population, but it may also reflect the effects of better health care and related factors, including nutrition, hygiene, educational status, and vaccination, on the course of the disease [21–24]. Comorbidity and lack of health maintenance in older SCD patients may be a factor explaining the age effect [22].

Clinical factors

A previous study showed a lower life expectancy among patients who experienced three or more painful crises a year [25]. Otherwise, despite the absence of overt symptoms, progressive tissue and organ damage may occur in patient with SCD [6, 25]. These findings were in line with our observation.

Hydroxyurea reduces the risk of vaso-occlusive events, neurologic events, and acute chest syndrome as well as the need for a blood transfusion and the frequency of hospitalization in patients with SCD [26, 27]. It has also been shown to reduce their mortality risk, particularly in pediatric patients [27]. However, there is no clear-cut evidence on the benefits of hydroxyurea treatment in terms of lowering the mortality risk in adult patients [19, 28]. A multicenter study of hydroxyurea showed that the annual mortality rate was 4.4 per 100 person-years in the 17.5 years follow-up cohort [10, 19]. This rate seems not different from the groups who received hydroxyurea less than 10 years. In addition, Elmariah et al. [19] reported a 25 % mortality at the end of the 10-year study. In our study, we found a positive effect of hydroxyurea on mortality. General feeling of this effect is mainly due to an increase in HbF. While studies of therapeutic options have included genetic approaches to elevating HbF levels [28, 29], whether higher HbF levels will reduce mortality is not pronounced. Our results were also parallel to previous findings. Other effects of hydroxyurea such as reducing the number of leukocytes or increasing the nitric oxide levels may be more prominent.

Transfusion therapy is frequently used in the prevention and management of SCD-related complications [25]. The results of many studies support the use of red cell exchange therapy in the management and prophylaxis of cerebrovascular events, as preoperative prophylaxis, and in treating acute chest syndrome, multiorgan failure, and pregnancy-related issues in SCD [16, 30–32]. But as with hydroxyurea therapy, whether this treatment option reduces SCD-related mortality is not clear. Whereas, we identified a reduction in mortality rate in pregnant women with SCD who underwent standard prophylactic red blood cell exchange protocol compared to the ones who did not receive exchange. A meta-analysis including five population-wide studies revealed variation in blood transfusion strategies may have influenced pregnancy outcomes [33]. These patients may be considered a special group among all SCD patients, and we routinely perform a standard prophylactic exchange protocol in this patient group. This observation may indicate that the obscure findings in literature arise from the absence of a standardized transfusion policy and making transfusion decision depending on individual concerns.

The prevalence of pulmonary hypertension in patients with SCD based on echocardiography screening is 20 to 30 %. Even mild pulmonary hypertension carries a 9- to 10-fold greater early mortality risk compared with patients with SCD who do not have pulmonary hypertension [34]. Thirty percent of our patients had pulmonary hypertension, but its relationship to mortality was not significant. These different findings may have been due to differences in the methods used to diagnose pulmonary hypertension. Pulmonary arterial pressure measured on echocardiography is obtained through indirect measurements. It is well known that, these measurements may show alterations if right ventricle or vena cava pressure changes due to reasons other than SCD. Therefore, the

recommended ideal method to measure pulmonary hypertension in adults who are vulnerable to these alterations due to increased tissue damage is the measurements done through tricuspid regurgitation velocity and obtaining the virtual pressure with catheterization [34, 35].

Chronic renal failure develops in 30 % of patients with SCD. Renal damage, beginning with microalbuminuria and progressing to end-stage renal failure, occurs in 10 to 50 % of patients with SCD and is an independent risk factor for cardiovascular disease [36].

Acute chest syndrome is the second leading cause of hospitalization of patients with SCD. It develops in 15 to 43 % of patients with SCD [16, 37, 38]. and accounts for 25 % of all deaths due to SCD. We found a statistically significant relationship between a history of acute chest syndrome and mortality in our study patients as well. Because acute chest syndrome is the most common cause of death in East Mediterranean Turkey, in order to avoid this and other complications, such as infection control, vaccination, and improved medical treatment, as well as the timely and correct administration of transfusion therapy [37, 38] are particularly important. It is the responsibility of primary care physicians to diagnose SCD and then refer these patients to the proper institutions. Secondary care includes the detection of tissue and organ damage and planning transfusion therapy, while tertiary care involves the management of complications. Central health authorities must continue to play a role in establishing communication between institutions, planning patient education, and facilitating patient transport procedures.

In pediatric patients, over 40 years ago, infections, primarily due to encapsulated bacteria, were the leading cause of death, followed by acute chest syndrome, and splenic sequestration crises [5]. In a more recent data, pulmonary complications, cerebrovascular events, and infection-related conditions were the most common causes of death in SCD [16]. In adults with SCD, death is most often due to chronic organ dysfunction including pulmonary complications, renal failure, and cerebrovascular events [39]. Sebastiani et al. [38] used a disease severity score system to predict the risk of death within 5 years in patients with SCD. In addition to pulmonary hypertension, renal failure, and leukocytosis, the severity of hemolytic anemia was identified as a laboratory value that should be included in estimating the risk of death.

In our study, the leading causes of death were found as acute chest syndrome and splenic sequestration consistently with literature. Differently, these were followed by prolonged painful crisis and hepatic failure. Prolonged painful crisis-related mortality was also reported in the ratio of 3 % by Lanzkron et al. [8]. Hepatic failure is not a frequently reported cause of mortality in SCD patients. We may suggest that it may develop due to genetic factors, mainly UGT1A1 gene encoding the enzyme UDP-glucuronosyl transferase-1 as reported by Kutlar [4].

Laboratory factors

In SCD, sickling erythrocytes and other inflammatory mediators activate endothelial cells. Erythrocytes and leukocytes then adhere to the activated endothelium, which in turn causes vascular stenosis and tissue ischemia. Chronic inflammation activates the coagulation system, such that the activated platelets and increased tissue factor levels result in vaso-occlusion [34, 35]. Elevated leukocyte counts and bilirubin levels are risk factors for early death in pediatric patients [16]. This finding was confirmed in our study, in which the relationship between elevated leukocyte count and mortality was significant. Elevated leukocyte count and low hemoglobin were also found to be associated with the survival.

Conclusion

The most common causes of mortality in our East Mediterranean study population were prolonged painful crisis and acute chest syndrome. Our findings highlight the importance of preventive actions to avoid complications of SCD, including the effective use of hydroxyurea treatment, infection prophylaxis, and supportive treatment. Once a disease complication has developed, the timing of interventional treatments, especially exchange transfusion, and the administration of intensive care are essential. A better understanding of the factors influencing mortality in patients with SCD will contribute to improved curative treatment options and a better determination of transplant indications.

Compliance with ethical standard This study was approved by the Institutional Medical and Health Sciences Experimental/Clinical Research Principles and Research Committee (project number: KA15/07). The required approvals for the collaborations in the study were obtained from the concerned departments and hospitals.

Conflict of interest The authors declare that they have no conflict of interest.

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