Evaluation Of Prevalence Of Thromboembolic Events In Patients With Sickle Cell Disease At King Abdulaziz Medical City, Riyadh, Kingdom Of Saudi Arabia

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ABSTRACT

Objectives Sickle cell disease is a monogenic autosomal recessive genetic disorder that associated with anemia, hypercoagulability and thrombosis. However, the prevalence and risk factors of SCD in the Saudi population is not well-established. This study was proposed to report the prevalence and risk factors associated with thromboembolic complications in patients with SCD visiting King Abdulaziz Medical City (KAMC) in Riyadh city, Kingdom of Saudi Arabia

Methodology: This quantitative retrospective Cross-sectional study was carried out by digging though 289 patient medical records who are attending KAMC between February 2016 and February 2019, and are clinically diagnosed as SCD patients. Review included demographics of patients, as well as their hematological laboratory examinations with or without thromboembolic complications.

Results: The results of sickling hemoglobin screening test and hemoglobin electrophoresis procedures clinically confirmed that all patients had positive results for homozygous sickle cell disease (HgbSS). Among those tested patients, 21 patients (7.2%) developed common thromboembolic events and had vaso-occlusive crisis, deep venous thrombosis (DVT), stroke and pulmonary embolism (PE). Analysis of coagulation parameters of the patients with these thromboembolic events showed significant reduction in the activated partial prothrombin time (aPTT) and international normalized ratio (INR) as compared to SCD patients without these thromboembolic events.

Conclusion: Patients with SCD are at a higher risk for developing pathological thrombus formation. The existence of elevated hemoglobin S (HgbS) level and hypercoagulable state significantly facilitates the progression of vascular thrombotic diseases within the SCD patients.

Keywords: SCD, thromboembolic events, hypercoagulable, Saudi Arabia.

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INTRODUCTION

Sickle cell disease (SCD) is one of the most predominant forms of hemoglobinopathies that is characterized by the presence of HgbS and is associated with increased rate of morbidity, disability and mortality, worldwide [1, 2]. The highest prevalence of SCD is found in the Middle East, Mediterranean, Africa, and Southeast Asia. In Saudi Arabia, the estimation of patients with SCD is varied according to the geographic locations with the reported highest prevalence in the Eastern and South-Western states [3-5]. Previous reports (before 2008)

have shown a high prevalence of SCD within the Kingdome of Saudi Arabia where the rates varied between 2% to 27% [3,4]. However, current a recent report from the Saudi premarital screening program states that approximately 4.2% of the population has SCD [5].

Current understanding for the pathophysiology of SCD revealed the mechanisms underlying this disorder. Within this view, it has been shown that a single point mutation of the β globin gene on chromosome 11 which replaces the amino acid, glutamic acid, with valine at the position 6 of the polypeptide chain is the major cause of the disease. Accordingly, this produces an abnormal hemoglobin form called HgbS which is the major mechanism causing SCD. The formation of HgbS alters deformability and elasticity of erythrocytes, thereby generating abnormal erythrocytes called sickle cells which have an abnormal sick shape when they are oxidized [2, 6]. As a consequence, the existence of these cells cause them to trap in the small blood vessels leading to stroke and internal organ damage, that are associated with episodic pain (i.e. crisis) and multiple clinical complications such as vascular complications, recurrent infections, bone necrosis, kidney problems, splenic sequestration and cardiopulmonary diseases [7-10]. In particular, thromboembolic complications observed in the SCD patients are attributed to the influence of abnormal hemoglobin molecular polymerization, leading to rigid and sickled erythrocytes, which potentially can promote vascular occlusive crisis [7-10]. Although the association between SCD and the progression of the vascular occlusion complications is widely studied, the etiology and pathophysiology of thromboembolic complications involved in SCD requires further research to increase the understanding of these events [11-13]. However, different mechanisms are hypothesized that might participate in thrombogenesis in patients with HgbS. This includes platelet activation, leukocyte recruitment, erythrocyte aggregation, endothelial dysfunction and coagulation hyperactivity [13-17]. Overall, the literature on sickle cell patients defined the impairment of hemostatic system in SCD as a critical modulator of thromboembolic complications in SCD.

Nonetheless, thromboembolic events are thought to be a serious health concern for the patients with SCD in both genders [11, 13]. The challenge to the clinicians is to recognize patients with SCD who are at risk of development of thromboembolism. Nevertheless, identifying the prevalence and risk factors of thromboembolic complications in those patients would provide much help to physicians in order to develop future preventive strategies [18]. This retrospective study was designed to determine the frequency prevalence of thromboembolic events among patients who were diagnosed with SCD that are attending KAMC in Riyadh, and determine the clinical characteristics of those patients who progress thrombosis versus to those without thrombosis development.

METHODS

This is a retrospective cross-sectional study of Saudi patients diagnosed with SCD from February 2016 to February 2019 at the department of hematology of KAMC, Riyadh, Saudi Arabia. A total of 289 medical records of patients with SCD were interrogated (167 males, 122 females). The clinical data of these patients such as demographic details, medical history, hematological and coagulation parameters were included. Sickle cell patients diagnosed with or without thrombotic complications between February 2016 and February 2019 were conducted; nevertheless, SCD patients who developed thromboembolic events before February 2016 were not included in this study. Furthermore, the sickle cell patients who under antiplatelet and/or anticoagulant treatment were excluded. The proposal of this study was approved by the research unit committee in the College of Applied Medical Sciences (COAMS) at the King Saud Bin Abdulaziz University for Health Sciences (KSAU-HS) and ethical approval was obtained from the Institutional Review Board (IRB) at King Abdullah International Medical Research Centre (KAIMRC) in the ministry of National Guard Health Affair, Riyadh, Kingdom of Saudi Arabia under the reference (SP19/209/R). Data were collected and analyzed by using the statistical program for GraphPad Prism software program version 6 (GraphPad, San Diego, CA, USA). Descriptive statistics were presented as mean ± standard deviation (SD) or expressed as percentage. Categorical data were analyzed using Chi-square test and a paired t-test was used for continuous variable analysis. Statistical significance was defined at p values less than 0.05 ($p<0.05$).

RESULTS

The present retrospective cross-section study reviewed a total of 289 (167 males and 122 females) medical records for patients diagnosed with SCD. The mean age of the subjects was 23 ± 6 years. The demographic and clinical characteristics of SCD patients without thromboembolic complications (n = 268) or with thromboembolic complications (n = 21) are shown in Table 1. All patients examined are clinically confirmed to have HgbSS by hemoglobin electrophoresis as documented in medical records of these patients. We found that the percentage of heart disease (14.3%), diabetes mellitus (14.3%), liver disease (9.5%) and hypertension (9.5%) are increased in the group of SCD patients with thrombosis compared to SCD patients without thrombosis (1.9%, 2.4%, 3.9% and 2.9%, respectively). Interestingly, splenomegaly was found to be more in the group of SCD patients that are without thrombosis (27.2%) compared to patients with thrombosis (23.8%). Overall**,** the comparative study between the SCD patients without or with SCD thromboembolic events exhibited that 21 (7.2%) patient's progressed thrombotic complications during the period of February 2016 to February 2019. When examining the events of thrombotic events in SCD patients as a whole, we found that DVT was highly frequent among SCD patients with (33.3%), while stroke was second highly prevalent with 28.6%. Four SCD patients (19.1%) patients had PE and 2 (9.5%) had myocardial infarction (MI), and 2 (9.5%) had peripheral occlusive vascular disease (POVD) (Figure 1). After that we compared the development of thromboembolic incidences with respect to the gender of SCD patients and found that males have higher frequency than females by 57% and 43% respectively, but the association this failed to reach statistical significance (Figure 2). Moreover, stroke was frequently reported in males more than females with 24% and 4.8% respectively, whilst POVD was high frequent in (9.5%) females compared with (0%) males (Figure 2).

Examination of the hemoglobin electrophoresis results of SCD patients showed that patients without thromboembolic complications had high levels of hemoglobin A (HgbA) and hemoglobin F (HgbF) compared with SCD patients with thromboembolic complications (Table 2). Furthermore, hemoglobin S (HgbS) was high level among those patients with thromboembolic events compared to SCD patients without thromboembolic events, but these associations failed to observe statistical significance (67.78 ± 2.42 vs. 63.7 ± 1.52, p = 0.16). Clinical hematological results showed that SCD patients with or without thromboembolic events had normocytic normochromic anemia (Table 2). Interestingly, low levels of hemoglobin, increased platelet count, increased LDL level were observed in SCD patients with thromboembolism when compared with sickle cell patients without thromboembolism but were not statistically significant.

Interestingly, low serum albumin levels were observed within SCD patients with thromboembolic events compared with those SCD patients without thromboembolic complications. Additionally, analysis of coagulation parameters showed a slight reduction in aPTT, and INR among SCD patients with thromboembolic events compared with SCD without thromboembolic events (Table 2).

Table 1: Baseline characteristics of patients with sickle cell disease

Patient characteristics	SCD without thrombosis (Mean ± SD), n= 268	SCD with thrombosis (Mean ± SD), n= 21
Gender (M/F)	131/97	12/9
Age (Years)	19.21 ± 8.75	28.44 ± 9.68
Splenomegaly (n %)	73 (27.2%)	5 (23.8%)
Liver disease, (n %)	8 (3.9%)	2 (9.5%)
Heart disease, (n %)	4 (1.9%)	3 (14.3%)
Renal disease, (n %)	5 (2.4%)	0.0
Essential thrombocythemia, (n %)	9 (4.4%)	1 (4.8%)
Diabetes Mellitus, (n %)	5 (2.4%)	3 (14.3%)
Hypertension, (n %)	6 (2.9%)	2 (9.5%)

SCD: Sickle cell disease, M: Male, F: Female. Data are represented as Mean ± SD or Data represented as %.

Table 2: Hematological and biochemistry data of patients with sickle cell disease

Parameter	SCD without thrombosis (Mean ± SD), n= 268	SCD with thrombosis (Mean ± SD), n= 21	*P* value
RBC Count ($\times10^{12}$/L)	3.35 ± 0.47	3.60 ± 1.00	0.485
Hemoglobin (g/dL)	10.90 ± 3.66	8.80 ± 1.93	0.126
Hct (%)	31.20 ± 11.41	34.80 ± 10.15	0.353
MCV (fL)	89.20 ± 7.33	92.70 ± 11.32	0.422
MCH (pg)	26.40 ± 4.60	28.90 ± 4.14	0.218
WBC Count ($\times10^{9}$/L)	7.50 ± 2.36	8.10 ± 2.68	0.602
Platelet Count ($\times10^{9}$/L)	374.87 ± 106.15	248.00 ± 146.16	0.067
HDL (mmol/L)	1.13 ± 0.32	1.26 ± 0.39	0.460
LDL (mmol/L)	2.37 ± 0.59	2.80 ± 0.73	0.1.61
Bilirubin (µmol\L)	15.72 ± 9.04	12.30 ± 7.41	0.368
Albumin (g\L)	34.82 ± 9.04	23.53 ± 6.39	0.004
HgbA (%)	35.19 ± 8.51	32.97 ± 8.19	0.560
$HgbA_2$ (%)	3.83 ± 1.22	3.77 ± 1.12	0.910
HgbF (%)	11.40 ± 4.45	10.08 ± 4.58	0.522
HgbS (%)	63.70 ± 4.76	67.78 ± 7.25	0.161
INR	1.57 ± 0.94	2.33 ± 1.33	0.170
APTT (Sec)	35.44 ± 6.69	37.77 ± 4.11	0.363

WBC: White blood cell, RBC: Red blood cell, Hct: Hematocrit, MCV: Mean cell volume, MCH: Mean cell hemoglobin, MCHC: Mean cell hemoglobin concentration, HgbA: Hemoglobin A, $HgbA_2$: Hemoglobin A_2, HgbF: Hemoglobin F, HgbS: Hemoglobin S, INR: (international normalized ratio), APTT: (activated partial thromboplastin time). Data are expressed as Mean ± SD, $p \leq 0.05$ was considered statistically significant, or Data represented as %

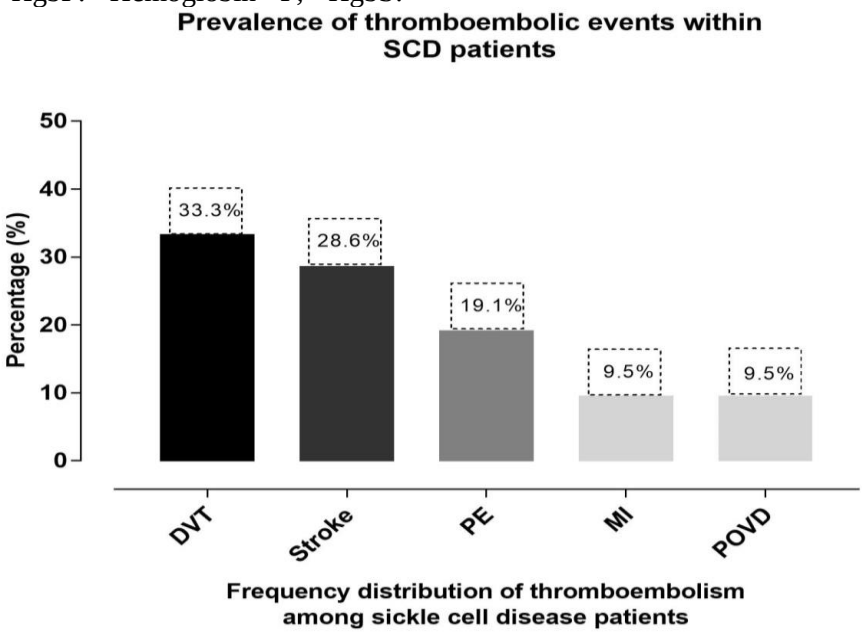

Figure 1: Prevalence of thrombotic events among SCD patients (both genders). Twenty-one out of 289 patients with sickle cell disease developed thrombotic complications over the period of three years (February 2016 to February 2019). 7 (33.3%) patients had DVT, 6 (28.6%) had stroke, 4 (19.1%) had PE, 2

(9.5%) had MI, and 2 (9.5%) had POVD. (Data represented as %).

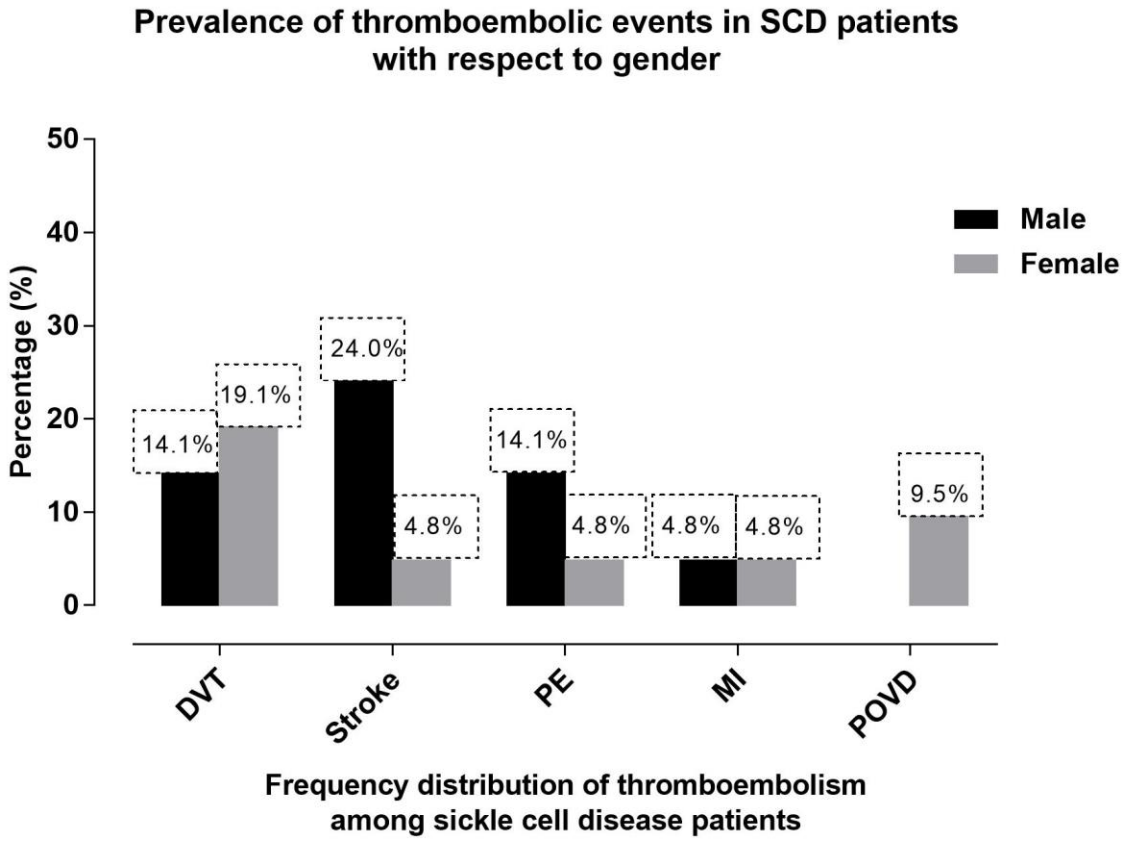

Figure 2: Frequency of thromboembolic events within SCD patients with respect to gender. Stroke was frequent in males more than females with 24% and 4.8% respectively, whilst DVT was high frequent in females with 19.1% compared with males (14.1%). PE was observed high prevalent in males (14.1%) than females (4.8%). Both gender had equally rates (4.8%) of MI, but POVD was observed among female patients. (Data represented as %).

DISCUSSION

Progression of thromboembolic complications and vaso-occlusive crises are the leading causes for increasing disability and mortality among the SCD patients [11, 19]. Venous and/or arterial thrombosis formation is prevalent in the SCD patients causing serious complications such as stroke, PE and DVT [13, 20, 21]. Up-to-date, several studies have hypothesized and provided substantial evidence to the contribution of platelet activation, leukocyte adhesion, endothelial dysfunction, and coagulation defects in mechanisms of thromboembolism in SCD [22-25]. The present study aimed to identify the prevalence of thromboembolic events and common risk factors which may contribute to thrombogenesis in some Saudi patients with SCD. Our data show that 21 patients (7.3%) out of our study sample developed thromboembolic events over a period of three years (February 2016-February 2019). The frequency of thromboembolic events among SCD patients was higher in males (57%) compared with females (43%) which was consistent with the previous findings by others [11]. We revealed that the median age for the SCD patients who had progressed thromboembolic events was 28 ± 9 years, which is considerably older than those who had not developed thromboembolic events. Our findings are consistent with previous study that showed 29.9 years was a median age for the SCD patients who developed thromboembolism, and suggested that the risk of thromboembolism is significantly augmented with increased age of those

patients when compared with universal population (>60 years) [26].

The current retrospective study demonstrated that SCD patients with clinical history of cardiovascular disease risk factors such as diabetes mellitus and hypertension significantly developed thromboembolism by 14.3% and 9.5% respectively. Moreover, SCD patients with the existence of splenomegaly, heart disease and liver disease were at a potential risk of thromboembolic complications. This is probably due to the fact that SCD patients with liver disease are at higher risk for thromboembolism due to defects in plasma coagulation factors that are synthesized in the liver. Therefore, those patients should be carefully supervised for the thrombus formation. Indeed, the presence of concomitant cardiovascular risk factor such as diabetes mellitus, arterial hypertension, obesity, health disorders, and liver disease in patients with SCD is highly associated with enhancement of thromboembolic complications [12, 18, 26]. We found that DVT, stroke and PE were more frequently among SCD patients with 33.3%, 28.6% and 19.1 respectively, while MI and PVOD were less frequently with 9.5%. Furthermore, stroke was frequently reported in males more than females with 24% and 4.8% respectively, whilst POVD was high frequent in females with 9.5% compared with males (0%). Previous studies stated that patients with SCD have high risk the development of thrombosis through its effect on endothelial dysfunction, coagulation cascades in particular coagulation factors activation and fibrinolysis and that could possibly have a bigger influence on the development of thromboembolic events [11, 18, 22].

Our study additionally found that the significant decreased in the levels of HgbA with the concomitant increase in the level of HgbS were frequently observed in SCD patients with thrombosis versus SCD patients without thrombosis. HgbS is well-known to induce the influence of hemoglobin polymerization causing rigidity of the erythrocytes with loss deformability which allows them to be trapped within the blood vessels, thus increasing whole blood viscosity [10, 27]. Austin et al. cited that HgbS is an independent risk factor for thrombus formation in SCD patients [26]. Consequently, increase levels of HgbS should be considered at higher risk factor for thromboembolic events in SCD patients. Collectively, we believe that presence of high levels of HgbS would augment the development of thromboembolism.

The analyzed hematological and biochemical results showed no clear association between the development of thromboembolic events and these laboratory parameters and the data did not reach statistical significance (Table 2). However, serum albumin levels were significantly reduced in SCD patients with thrombosis particularly those diagnosed with diabetes mellitus when compared with SCD patients without thrombosis. As reported in previous studies, diminished concentration of albumin in the existence of concomitant thromboembolic risk factor such as diabetes mellitus critically enhanced risk of arterial and/or venous thrombus formation [28, 29]. Moreover, patients with diabetes mellitus have been shown to have liver problems and impaired liver synthesis of coagulation factors. Therefore, measurement of albumin levels in the serum of SCD patients specifically those with existing risk factor for thrombosis such as diabetes mellitus could help in recognizing patients at risk of thromboembolic complications.

Our study showed that dropped platelet number were reported in SCD patients with thrombosis when compared to SCD without thrombosis (374.87 ± 106.15 versus 248.0 ± 146.16), but no statistical significance observed. It could be explained that activation and consumption of circulating platelets in vivo leading to a reduction in platelet count among SCD patients with thrombosis. Moreover, the present data demonstrated that a shorter INR (extrinsic coagulation pathway) and aPTT (intrinsic coagulation pathway) in SCD patients with thrombosis compared with SCD patients without thrombosis in which may indicate to hypercoagulability that occurred in SCD patients with thrombosis. Hypercoagulability is defined as an imbalance of anti-versus coagulation system, resulting in the development of thrombogenic phenotype [30]. In general, a defective component of hemostasis system including coagulation pathways, platelets and endothelial cells in SCD has been identified to contribute to mechanisms of thrombogenesis [31, 32]. Overall, this is in favor of our arguments that SCD with an underlying diabetic mellitus or liver disease is at high risk to develop alterations in coagulation parameters.

Our conclusion is that thromboembolic complications are more common in Saudi SCD patients, in particular

those with diabetic mellitus, liver disorder, heart disease, and hypertension, etc. Early detection and diagnosis of these high risks SCD patients should be implemented as these patients are at risk of arterial and/or venous thrombosis. This would be vital approaches to clinicians to help prevent the development of serious thromboembolic complications.

Conflict-of-interest disclosure
The authors declare no competing financial interests.

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Authorship
NMA contributed in conception of the study, data analysis, and wrote the manuscript. ME, RSA and MMA provided intellectual input, review and editing the manuscript. Overall, all authors read and approval the final draft of manuscript.

REFERENCES

1. Steinberg MH. 6 Pathophysiology of sickle cell disease. Baillière's clinical haematology. 1998;11(1):163-184.
2. Embury SH. The clinical pathophysiology of sickle cell disease. Annual review of medicine. 1986;37(1):361-376.
3. Lehmann H, Maranjian G, Mourant AE. Distribution of sickle-cell hemoglobin in Saudi Arabia. Nature. 1963;198:492-493.
4. Al-Qurashi MM, El-Mouzan MI, Al-Herbish AS, Al-Salloum AA, Al-Omar AA. The prevalence of sickle cell disease in Saudi children and adolescents. Saudi Med J. 2008;29(10):1480-1483.
5. Jastaniah W. Epidemiology of sickle cell disease in Saudi Arabia. Annals of Saudi medicine. 2011;31(3):289-293.
6. Steinberg MH, Rodgers GP. Pathophysiology of sickle cell disease: role of cellular and genetic modifiers. Seminars in hematology. 2001;38(4):299-306.
7. Francis RJ, Johnson CS. Vascular occlusion in sickle cell disease: current concepts and unanswered questions. blood. 1991;77:1405-1414.
8. Flint J, Harding RM, Boyce AJ, Clegg JB. 1 The population genetics of the haemoglobinopathies. Baillière's clinical haematology. 1998;11(1):1-51.
9. El-Hazmi MA, Al-Hazmi AM, Warsy AS. Sickle cell disease in Middle East Arab countries. The Indian journal of medical research. 2011;134(5):597-610.
10. Bunn HF. Pathogenesis and treatment of sickle cell disease. New England Journal of Medicine. 1997;337(11):762-769.
11. Naik RP, Streiff MB, Haywood Jr C, Nelson JA, Lanzkron S. Venous thromboembolism in adults with sickle cell disease: a serious and under-recognized complication. The American journal of medicine. 2013;126(5):443-449.
12. Gladwin MT, Sachdev V. Cardiovascular abnormalities in sickle cell disease. Journal of the American College of Cardiology. 2012;59(13):1123-1133.
13. Stein PD, Beemath A, Meyers FA, Skaf E, Olson RE. Deep venous thrombosis and pulmonary embolism in hospitalized patients with sickle cell disease. The American journal of medicine. 2006;119(10):897. e811.
14. De Franceschi L, Cappellini MD, Olivieri O. Thrombosis and sickle cell disease. Seminars in thrombosis and hemostasis. 2011;37(03):226-236.
15. Green D, Scott JP. Is sickle cell crisis a thrombotic event? American journal of hematology. 1986;23(4):317-321.
16. Ataga KI, Orringer EP. Hypercoagulability in sickle cell disease: a curious paradox. The American journal of medicine. 2003;115(9):721-728.
17. Lim MY, Ataga KI, Key NS. Hemostatic abnormalities in sickle cell disease. Current opinion in hematology. 2013;20(5):472-477.
18. Qari M, Dier U, Mousa S. Biomarkers of inflammation, growth factor, and coagulation

activation in patients with sickle cell disease. Clinical and Applied Thrombosis/Hemostasis. 2012;18(2):195-200.

19. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, et al. Mortality in sickle cell disease--life expectancy and risk factors for early death. New England Journal of Medicine. 1994;330(23):1639-1644.
20. Verduzco LA, Nathan DG. Sickle cell disease and stroke. Blood, The Journal of the American Society of Hematology. 2009;114(25):5117-5125.
21. Strouse JJ, Lanzkron S, Urrutia V. The epidemiology, evaluation and treatment of stroke in adults with sickle cell disease. Expert review of hematology. 2011;4(6):597-606.
22. Rickles FR, O'Leary DS. Role of coagulation system in pathophysiology of sickle cell disease. Archives of internal medicine. 1974;133(4):635-641.
23. Kaul D, Nagel R, Chen D, Tsai H. Sickle erythrocyte-endothelial interactions in microcirculation: the role of von Willebrand factor and implications for vasoocclusion. Blood. 1993;81(9):2429-2438.
24. Hidalgo A, Chang J, Jang J-E, Peired AJ, Chiang EY, Frenette PS. Heterotypic interactions enabled by polarized neutrophil microdomains mediate thromboinflammatory injury. Nature medicine. 2009;15(4):384-391.
25. Kenny M, George A, Stuart J. Platelet hyperactivity in sickle-cell disease: a consequence of hyposplenism. Journal of clinical pathology. 1980;33(7):622-625.
26. Austin H, Key NS, Benson JM, Lally C, Dowling NF, Whitsett C, et al. Sickle cell trait and the risk of venous thromboembolism among blacks. Blood, The Journal of the American Society of Hematology. 2007;110(3):908-912.
27. Zhou Z, Behymer M, Guchhait P. Role of extracellular hemoglobin in thrombosis and vascular occlusion in patients with sickle cell anemia. Anemia. 2010;2011:918-916.
28. Djoussé L, Rothman KJ, Cupples LA, Levy D, Ellison RC. Serum albumin and risk of myocardial infarction and all-cause mortality in the Framingham Offspring Study. Circulation. 2002;106(23):2919-2924.
29. Gillum RF, Makuc DM. Serum albumin, coronary heart disease, and death. American heart journal. 1992;123(2):507-513.
30. Jackson SP. The growing complexity of platelet aggregation. Blood. 2007;109(12):5087-5095.
31. Jackson SP. Arterial thrombosis [mdash] insidious, unpredictable and deadly. Nature Medicine. 2011;17(11):1423-1436.
32. Jackson SP, Nesbitt WS, Kulkarni S. Signaling events underlying thrombus formation. Thrombosis and Haemostasis. 2003;1(7):1602-1612.