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Abdullah Al-Reesi
AUTEUR DE LA THÈSE / AUTHOR OF THESIS

M.A. (Epidemiology)
GRADE / DEGREE

Department of Epidemiology and Community Medicine
FACULTÉ, ÉCOLE, DÉPARTEMENT / FACULTY, SCHOOL, DEPARTMENT

Sickle Cell Disease in the Emergency Department
Predictors of Adverse Outcomes
A Prospective Cohort Study

TITRE DE LA THÈSE / TITLE OF THESIS

I. Stiell
DIRECTEUR (DIRECTRICE) DE LA THÈSE / THESIS SUPERVISOR

G. Wells
CO-DIRECTEUR (CO-DIRECTRICE) DE LA THÈSE / THESIS CO-SUPERVISOR

EXAMINATEURS (EXAMINATRICES) DE LA THÈSE / THESIS EXAMINERS

R. Nair

P. Wells

Gary W. Slater
Le Doyen de la Faculté des études supérieures et postdoctorales / Dean of the Faculty of Graduate and Postdoctoral Studies

Sickle Cell Disease in the Emergency Department

Predictors of Adverse Outcomes

A Prospective Cohort Study

By

Abdullah Al Reesi MD FRCPC

Thesis submitted to the Faculty of Graduate and Postdoctoral Studies

in partial fulfillment of the requirements for the

MSc Degree in Epidemiology

Thesis supervisors:

Ian G Stiell MD MSc FRCPC

George A Wells PhD

Alan Tinmouth MD MSc FRCPC

University of Ottawa

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ABSTRACT

Introduction:

Current evidence does not provide a clear risk stratification strategy for sickle cell disease patients in the emergency department (ED). The goal of this study was to develop a better understanding of the clinical features among patients with sickle cell disease and to determine the risk factors for short term adverse events.

Methods:

We conducted a prospective cohort study of sickle cell disease patients presenting to a tertiary care ED over six consecutive months. All patients were assessed by emergency physicians during the ED visit. All the patients had a 2 week structured telephone follow-up or a chart review if they had a repeat ED visit within 2 weeks or admitted. The adverse outcomes were classified as a clinically significant outcome (death, cerebrovascular accidents, acute chest syndrome, sepsis, hyper-hemolytic crisis and exchange blood transfusion) or not. We also classified patients as having acute chest syndrome or not. We analyzed the predictors of adverse outcomes using descriptive statistics and multiple logistic regression.

Results:

Over six consecutive months, we enrolled 732 patients. Seventy-five patients had a clinically significant outcome and 42 had acute chest syndrome. Using multivariate analysis, we found nine statistically significant predictors of a clinically significant adverse outcome: a prolonged painful episode (OR 10.1; 95%CI 5.3-19.3), age less than 8 years (OR 2.4; 95%CI 1.001 -5.9), oxygen saturation less than 96% (OR 3.9; 95%CI 1.6-10.9), patient appearing toxic (OR 7.8; 95%CI 2.2-27.2), presence of chest crackles

(OR 6.5; 95%CI 2.3-18.6), splenomegaly (OR 2.6; 95%CI 1.2-5.5), local limb tenderness (OR 0.2; 95%CI 0.08-0.7), hemoglobin less than 7 g/dL (OR 3.6; 95%CI 1.1-11.6), reticulocyte count more than 15% (OR 4.0; 95%CI 1.4-11.5). Using multivariate analysis, we found seven statistically significant predictors of acute chest syndrome: a prolonged painful episode (OR 22.0; 95%CI 8.7-55.3), oxygen saturation less than 92% (OR 17.7; 95%CI 1.7-184.9), history of cough (OR 4.5; 95%CI 1.7-12.0), history of pneumococcal vaccine (OR 0.33; 95%CI 0.11-0.98), presence of chest crackles (OR 9.5; 95%CI 2.6-34.7), local limb tenderness (OR 0.20; 95%CI 0.05-0.80), and reticulocyte count more than 15% (OR 4.9; 95%CI 1.2-19.7).

Conclusion:

Our study of a tertiary hospital emergency department found nine identifiable variables which can help to predict the possibility of developing a clinically significant outcome. We also found seven identifiable variables which can help to predict the possibility of developing acute chest syndrome. This might be used in the future to risk stratify the sickle cell disease patients who presents to the emergency department and develop strategies to prevent those adverse outcomes.

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Table of Contents

APPENDICES .....

List of Tables and Figures

Chapter 1: Background and Review of Literature

Sickle cell anemia is an inherited disorder transmitted as an autosomal recessive trait that causes an abnormality of the globin genes in hemoglobin. When both parental genes carry the same defect, the person is homozygous for hemoglobin S, i.e., HbSS, and manifests the disorder. When exposed to a decrease in oxygen, hemoglobin S becomes viscous. This causes the red cells to become crescent-shaped (sickling), rigid, sticky, and fragile. When they clump together, circulation through the capillaries is impeded; causing obstruction, tissue hypoxia, and further sickling.[1] This leads to various clinical presentations and could causes serious complications (e.g. organ failure).

Patients with sickle cell disease presents with multiple complaints at the emergency department. On admission, they undergo extensive laboratory and radiologic testing. After discharge, there is potential for deterioration that may lead to serious adverse outcomes. Current evidence does not provide a clear risk stratification strategy for those likely to have adverse outcomes. Hence we conducted a prospective cohort study in tertiary center emergency department to develop a better understanding of the clinical features among patients with sickle cell disease and to determine the risk factors for short term adverse events in order to contribute to future management strategies.

1.1.1 Introduction to Sickle Cell Disease

1.1.2 Pathogenesis of Sickle Cell Disease and Epidemiology:-

Hemoglobin S (HbS) results from the substitution of a valine for glutamic acid as the sixth amino acid of the beta globin chain. This results in hemoglobin which is poorly soluble under certain stressors like low oxygenation tension. [2] Deoxy HbS polymerization in conjunction with changes in red cell membrane structure and function,

disordered cell volume control, and increased adherence to vascular endothelium leads to vaso-occlusive process.[3] This is the whole mark of sickle cell disease. This results in tissue ischemia which leads to acute and chronic organ dysfunction.

The geographic distribution of Sickle cell disease genes includes all of Africa, the Mediterranean, Middle East, and India and the Caribbean and parts of Central and South America. Approximately 2000 affected infants are born in the United States each year which makes it the most prevalent disorder identified by neonatal blood screening.[4] Sickle cell disease has significant morbidity which could be insidious, as with sickle nephropathy, cardiomyopathy, pulmonary hypertension and splenic infarction or acute episodes or crises, as stroke, sepsis, hyper-hemolytic crisis, acute chest syndrome and acute painful crisis. Patients with sickle cell disease have also reduced survival. Quinn et al reported an overall survival of 86% and a death rate of 0.59 per 100 patient-years for children who had SS by the age of 18 years.[5]

1. 1.2 Historical Background of Sickle Cell Disease:-

In 1910, Herrick described the first patient with sickle cell disease.[6] Thirty-six years later; Beet discovered that sickle cell disease patients have an increased resistance to malaria. Linus Pauling and coworkers showed sickle cell disease to be the first genetic disease linked to a mutation of a specific protein. It was originally thought that the Arabian Peninsula (subsequently spreading to Asia and Africa) was the origin of the mutation that led to the sickle cell gene. Independent mutations have been postulated as leading to various types of sickle cell hemoglobins[7], and occurring approximately between 70 000 to 150 000 years ago.

1.1.3 Sickle Cell Disease Genetics:-

Sickle-cell disease is a group of genetic disorders caused by sickle hemoglobin (Hgb S or Hb S). The sickle cell diseases are inherited in an autosomal co dominant manner. The sickle cell trait results from inheritance of Hb S from one parent and Hb A (normal Hb) from the other parent. Sickle cell anemia (Hb SS) results from inheritance of Hb S genes from both parents. A subtype of Hb SS disease involves coinheritance of the α-thalassemia gene. Another variant of sickle cell disease is Hb SC disease. In this variant, the child inherits one Hb S gene from one parent and one Hb C gene from the other parent. Sickle cell β-thalassemia involves inheritance of one Hb S from one parent and the thalassemia gene (β-thal gene) from the other parent.[8] Figure 1 shows the genetic variables in sickle cell disease.

1.1.4 Diagnosis of Sickle Cell Disease:-

Hemoglobin electrophoresis is used to establish and confirm the diagnosis of sickle cell disease. It can also differentiate subgroups of the disease. The 5-minute solubility test, Sickledex, is a screening tool that can exclude sickle cell at infants aged older than 6 months who do not have severe anemia or high levels of Hb F.[77] The test yields positive results if the Hb S level is greater than 10%. However, it does not differentiate among Hb SS, Hb SA, Hb SC, and Hb Sβthal. It also cannot detect carriers of Hb C Hb D or thalassemias.[9]

1.1.5 Clinical Features of Sickle Cell Disease:-

1.1.5.1 Age of Onset: In most patients, the clinical features of sickle cell disease first appear during the initial 8 years of life. This is best illustrated in a study of 305 children in whom the disease was diagnosed at birth.[5] Specific symptoms were present by

age 6 months in 6% of the cohort and developed by the end of the first year of life in 32%. By the age of 8 years, 96% of the patients developed symptoms related to sickle cell disease. Dactylitis, defined as painful swelling of the feet and hands during the first several years of life in children with sickle cell anemia, was the most common initial symptom and was noted in 40% of the group overall and in 50% during the first 2 years.[10]

1.1.5.2 Acute Painful Episodes: The clinical manifestations of sickle cell disease are summarized in Table 1. Acute painful episodes (previously known as *sickle cell crisis*) are the most common clinical presentation. These episodes are also the most common cause for admission to the hospital and account for 80% of all acute admissions.[11] Pain can affect different parts of the body, either in isolation or in combination with other presentations. There is considerable variability in the severity and frequency of the painful episodes. Uncomplicated acute pain is self-limited and generally lasts several hours to a few days; however, it can persist or recur and can migrate from one site to another. The "pain rate" (episodes per year) is also a measure of clinical severity of the disease and correlates with early death in patients older than 20 years of age with sickle cell anemia.[12]

1.1.6 Life-threatening Complications of Sickle Cell Disease in the Emergency Department:-

While painful crisis is the most common presentation, infection is the most common cause of death in patients with sickle cell anemia. Specifically, pneumococcal sepsis is a leading cause of death among infants with sickle cell anemia. Other potential causes for death in sickle cell disease patients include: osteomyelitis, cerebrovascular accidents, splenic sequestration crisis, hyperhemolytic crisis, acute chest syndrome and

acute myocardial infarction. The overall rate of stroke was 0.85/100 patient-years.[31] The incidence rate for splenic sequestration crisis is 11.3 per 100 whereas the incidence of acute chest syndrome was 12.8/100 patient-years.[60]

1.1.6.1 Infections: Sickle cell disease patients are immunocompromised owing to functional asplenia. The spleen cannot filter the invasive organisms beginning as early as 4 months of age; eventually, the spleen becomes nonfunctional as the result of repeated infarctions. Dysfunctional IgG and IgM antibody response, a lack of splenic clearance, defects in alternative pathway fixation of complement, and opsonophagocytic dysfunction play a role in the predisposition to invasive infection from polysaccharide-encapsulated organisms.[13] Patients with sickle cell disease present to the emergency department with fever, which could be the result of minor infections or sepsis. Establishing which patients are likely to develop sepsis is difficult. Appendix B shows the infection and its associated micro-organisms.

1.1.6.2 Bacteremia and Sepsis: *Streptococcus pneumonia* is the most important cause of death in sickle cell disease patients.[14, 15] It is associated with a mortality rate of 20% to 50%.[16] *Haemophilus influenzae* type b has been the second most-common organism responsible for bacteremia in children with sickle cell disease (10%-25% of episodes).[17] The incidence of both infections has declined since the introduction of vaccination and prophylactic antibiotics.

1.1.6.3 Bacterial Pneumonia: In one study, bacterial pneumonia was associated with acute chest syndrome in 30% of the patients. Of the isolated organisms, 30% were due to *C. pneumoniae*, 21% to *Mycoplasma pneumoniae*, 10% to Respiratory Syncytial Virus(RSV), 4% to *Staphylococcus aureus*, and 3% to *Streptococcus pneumonia.*[18]

1.1.6.4 Meningitis: Meningitis in sickle cell disease patients is most commonly caused by *Streptococcus pneumonia* followed by *Haemophilus influenzae* type b. *Neisseria meningitidis*, classically infects individuals with poor or absent splenic function but is not a common pathogen in sickle cell disease.

1.1.6.5 Osteomyelitis: Patients with sickle cell disease have recurrent bone infarction. This predisposes them to osteomyelitis. The most common offending organisms are Salmonella species followed by infections stemming from *Staphylococcus aureus.* Because the clinical features overlap, distinguishing osteomyelitis from a simple painful crisis could be difficult during the acute phase.

1.1.6.6 Cerebrovascular Events: Cerebrovascular accident (CVA) is a major complication of sickle cell disease. The incidence of CVA was 0.61 per 100 patient-years. The incidence of infarctive CVA was lowest in sickle cell SS patients 20 to 29 years of age and higher in children and older patients. Risk factors for infarctive stroke included prior transient ischemic attack, low steady-state hemoglobin concentration and rate of and recent episode of acute chest syndrome, and elevated systolic blood pressure. Hemorrhagic stroke was associated with low steady-state hemoglobin and high leukocyte count.[19]

1.1.6.7 Splenic Sequestration Crisis: A vaso-occlusive crisis in the spleen results in pooling of blood in the spleen, which results in massive spleen enlargement and hypovolemic shock. This could lead to death if aggressive fluid resuscitation is not done quickly. Splenic sequestration crisis is associated with a 10% mortality rate. Recurrences occur in 49% of survivors of first attacks; this led to adoption of doing a routine splenectomy after the first or second attack.[20]

1.1.6.8 Aplastic Crisis: A transit arrest in the synthesis of red blood cells occurs in some patients with sickle cell disease, which could lead to severe anemia and death. The patients usually presents with increased weakness and malaise. Skin rash and fever associated with parvovirus B19 might develop but commonly absent. This leads to low Hb and inappropriately low reticulocyte (the newly synthesized red blood cells) counts. Parvovirus B19 infection has been found in most patients having an aplastic crisis.[21-22]

1.1.6.9 Hyperhemolytic Crisis: Accelerated hemolysis leads to drop in Hb and acute anemia. These patients usually need a blood transfusion. Multiple causes have been identified including viruses, drugs and previous blood transfusions.[23]

1.1.6.10 Acute Chest Syndrome: Acute chest syndrome is a clinical entity that can lead to respiratory failure and death. It is the second leading cause of death in sickle cell disease patients. Acute chest syndrome can result from infection (pneumonia), vaso-occlusive crisis in the lungs, or fat pulmonary emboli. The clinical diagnosis is established by the following criteria: a new pulmonary infiltrate detected by chest radiograph involving at least 1 complete lung segment not consistent with the appearance of atelectasis *and* 1 or more of the following signs or symptoms: chest pain, temperature > 38.5°C , tachypnea, wheezing, cough, or the appearance of increased work of breathing.[24]

1.1.6.11 Acute Myocardial Infarction: Acute myocardial infarction without atherosclerosis has been documented in case reports and in the autopsies of sickle cell disease patients. Gross and microscopic findings consistent with acute and healed

myocardial infarction were found in 7 of 72 consecutive hearts (9.7%) from patients with sickle cell disease studied after autopsy between 1950 and 1982.[25]

1.1.7 Treatment of Patients with Sickle Cell Disease:-

Management of patients with sickle cell disease requires a multidisciplinary approach. Management could be divided into treatment of the acute episodes and continuous management. We will focus on acute management as it relates to emergency department patients.

1.1.7.1 Management of the Painful Episodes: Patients presenting with pain to the emergency department should be managed with optimal hydration using oral or intravenous fluid resuscitation (particularly in children); and aggressive pain relief using opioids, other analgesics, or other modalities.[26] Optimal pain management is crucial. An opioid analgesic is the treatment of choice for pain. It should be titrated to response. Adjuvant treatment includes nonsteroidal anti-inflammatory drugs, steroids, and inhaled nitric oxide. Some experts recommend small-dose ketamine for patients resistant to opioid analgesics. The usual starting dose for opioid analgesia is shown in Appendix A.

1.1.7.2 Management of Febrile patients: Fever is most commonly caused by infections. Sickle cell disease patients with fever should have a complete evaluation including a complete blood count, blood cultures, and radiologic investigations. Specific infections should be treated with antibiotics as recommended. Febrile episodes without a definitive cause are challenging. One study categorized patients as high-risk and low-risk patients. Low-risk patients were managed as outpatients with antibiotics. None of these

patients developed sepsis. This allowed the discharge of a subgroup of patients with fever without causing sepsis.[27]

1.1.7.3 Management of Anemia Episodes: Patients with sickle cell disease have a low baseline Hb. Acute anemic episodes should be managed with blood transfusions as indicated. Little evidence exists on the indications for blood transfusion. Acute transfusion is indicated in severe acute anemia or hypovolemia secondary to splenic sequestration crisis. Exchange transfusion is indicated in patients with CVAs and some episodes of acute chest syndrome.

1.1.7.4. Other Treatment Modalities: : Prophylactic penicillin is indicated to prevent streptococcal infection in children aged younger than 5 years.[28, 29] Vaccination against *Haemophilus influenzae* type b, Streptococcus pneumonia, hepatitis B virus, and influenza should be routinely administered to sickle cell disease patients.[30] Hydroxyurea is a medication given to increase fetal Hb level and reduce the sickle Hb. One randomized controlled trial in adults found that hydroxyurea reduced the incidence of a painful crisis, acute chest syndrome, and the need for blood transfusion over a mean of 21 months compared with placebo. It found no significant difference in the rates of stroke, hepatic sequestration, and mortality between hydroxyurea and placebo. Other randomized controlled trials in children found that hydroxyurea reduced the duration of hospital stay compared with placebo.[31,32,33] A randomized control trial found that taking hydroxyurea was associated with a 40% reduction in mortality ($P = 0.04$).[34]

1.1.8 Statement of the Problem in the Emergency Department:-

Sickle cell disease patients present to the emergency department with various clinical problems. The most common presentations are painful vaso-occlusive crises. The

painful episodes vary from one patient to another. A large prospective study followed 3578 patients and found that the average rate was 0.8 episode per patient-year in sickle cell anemia, 1.0 episode per patient-year in sickle beta 0-thalassemia, and 0.4 episode per patient-year in hemoglobin SC disease and sickle beta(+)-thalassemia.[12] There is considerable variability in the severity and frequency of acute episodes. One third of patients rarely have pain, one third have more than 2 to 6 pain crises per year and one third have more than 6 hospitalizations per year.[35] It is difficult to predict which patients are likely to have one episode and which patients are likely to have multiple episodes.

Patients with fever are a challenging problem in the emergency department. There is potential for these patients to develop sepsis. There is no available data on the frequency of patients presenting with fever to the emergency department. Small studies categorized patients with fever into low risk of developing sepsis and high risk based on clinical and laboratory criteria. Antibiotics were still recommended for the low risk patients.[27] Overall survival of patients with sickle cell disease is reduced with a median survival of 42 years for men and 48 years for women[36]. Death is a potential adverse outcome in patients with SCD patients. Long terms studies were able to find predictors for death in such patients.[37] However, there are no studies to find predictors of death in patients presented to the emergency department. There is also no available data regarding death at the study site. Emergency physicians also find themselves in dilemma regarding the best and safe management and disposition for those patients. Patients who presents with painful episodes could potentially die or develop adverse outcomes. Patients with fever could be having sepsis which might lead to death. The risk of sepsis or meningitis is 12.5% from these infections for each individual, and the case fatality ratios were 35% and

10%, respectively.[38] Finding a safe stratification strategy for such patients is out most important. Sickle cell patients are frequent visitors to the emergency department at the study site (the Sultan Qaboos University Hospital) with 3600 visits annually. Frequent and prolonged hospitalizations are a risk factor for early mortality in patients with sickle cell disease.[39] However; it is also impractical to admit all patients with frequent visits to the emergency department to prevent adverse outcomes.

1.1.9 Statement of the Problem at the Study Site:-

Oman is a Middle Eastern country in the east of Arabia on the Indian Ocean with a population of two and a half million people. The estimated prevalence of sickle cell disease is of 11.7 cases per 10000. The estimated carrier rate for the sickle cell gene is 5.8% of the population.[40] In comparison, there are approximately 1 in 600 carrier cases of sickle disease gene among the black population in the United States .[31] There is 25% repeat emergency department visits within 2 weeks at the study site mostly related to painful episodes. There are no readily available data on emergency department visits of these patients nor are there data on repeat visits in patients with problems related to sickle cell disease. Problems related to sickle cell disease are frequently encountered in the emergency department at the Sultan Qaboos University Hospital, with 3600 patient visits per year. There are no previous studies that estimate return visits or potential adverse outcomes after discharge from the emergency department.

1.2 Prediction of Adverse Outcomes and Review of the Literature:-

Sickle cell disease patients pose a challenge to physicians. It is a chronic lifelong disease with no available cure. Physicians are likely to encounter those patients and should be aware of the complications. Predictive models of the patients who are likely to

develop adverse outcomes have been studied for some of the adverse outcomes. However, all of the studies are either office based or in-hospital. All the studies are long term follow-up and none addressed the emergency patients specifically. The predictive models for mortality, CVA, acute chest syndrome, and sepsis are discussed below.

1.2.1 Predictive Variables for Mortality:-

Quinn et al followed a cohort of sickle cell disease patients from the neonatal period until the age of 18 years.[5] They included 711 subjects. Twenty-five subjects died; mean age at death was 5.6 years. Five patients died from infection. The overall rates of death were 0.59/100 patient-years. They also found that childhood mortality from sickle cell disease was decreasing, the mean age at death was increasing, and a smaller proportion of deaths were from infection. A health record review following the clinical course of 392 children with sickle cell disease from infancy to approximately age 10 identified 3 previously identified significant predictors of long-term adverse outcomes: dactylitis (RR=2.6), hemoglobin less than 7 g/dL (RR=2.5), and leukocytosis in the absence of infection (RR=1.8).[41] Another, larger study followed 3764 patients and revealed that acute chest syndrome, renal failure, seizures, a baseline white cell count above 15 000 cells/mm^3, and a low level of fetal hemoglobin were associated with an increased risk of early death.[42] The causes of death were revealed in an autopsy study of 306 patients. The most common cause of death for all sickle variants and for all age groups was infection (48%). Other causes of death included stroke (9.8%), therapy complications (7.0%), splenic sequestration (6.6%), pulmonary emboli/thrombi (4.9%), renal failure (4.1%), pulmonary hypertension (2.9%), hepatic failure (0.8%), massive hemolysis/red cell aplasia (0.4%), and left ventricular failure (0.4%). Death was

frequently sudden and unexpected (40.8%) or occurred within 24 hours after presentation (28.4%) and was usually associated with acute events (63.3%).[43] There are no studies describing predictor variables for patients presenting to emergency departments.

1.2.2 Cerebrovascular Accident (CVA) Predictor Variables:-

The risk of a CVA varies with the genotype. The highest rates of prevalence of CVA (4.01%) and incidence (0.61 per 100 patient-years) were in sickle cell anemia (SS) patients, but CVA occurred in all common genotypes. Five risk factors of having infarctive stroke were identified: prior transient ischemic attack (RR=56.0), low steady state hemoglobin (RR=1.9 per 1 g/dL decrease), an episode of acute chest syndrome within the previous 2 weeks (RR=7.0), rate of acute chest syndrome (RR=per event per year), and elevated systolic blood pressure (RR 1.3 per 10 mg increase).[14]

Transfusion greatly reduces the risk of a first stroke in children with sickle cell anemia who have abnormal results on transcranial Doppler ultrasonography. A prophylactic chronic transfusion program with a goal HbS of less than 30% of total hemoglobin reduces the risk of stroke by 92%. [44] It is unknown whether fluid therapy reduces the risk of stroke. There are no known data regarding which patients are likely to develop stroke after discharge from the emergency department.

1.2.3 Predictors for Bacteremia and Sepsis:-

Febrile patients without a source ; no cause for the fever could be found from the history, physical examination ,and basic investigations; are a major challenge to emergency department physicians. Patients could develop overwhelming sepsis and die. Admitting all patients with fever is not a practical solution for these patients, especially if there is high prevalence of sickle cell disease in the community. Two studies have shown

a safe strategy for managing a subset of patients. Febrile patients were divided into those with a low risk and those with a high risk of developing sepsis. Low risk patients included those with sickle cell anemia or sickle cell-beta (0) thalassemia with temperatures less than 40°C who were taking prophylactic penicillin and those with HbSC disease or sickle cell-beta (+) thalassemia with temperatures greater than 38.5°C. These patients were managed with intramuscular ceftriaxone and close follow-up.[27, 45]

1.2.3 Acute Chest Syndrome (ACS):-

Acute chest syndrome is defined by a new pulmonary infiltrate on radiograph. It has a higher incidence in patients with homozygous sickle cell disease (SS; 12.8/100 patient-years) and in patients with sickle cell-beta(0) -thalassemic (9.4/100 patient-years), and a lower incidence in patients with hemoglobin (Hb) SC disease (5.2/100 patient-years) and patients with sickle cell-beta(+) thalassemia (3.9/100 patient-years). The incidence was strongly but inversely related to age, being highest in children 2 to 4 years of age (25.3/100 patient-years in SS) and decreasing gradually to its lowest value in adults (8.8/100 patient-years in SS).[46] The National Acute Chest Syndrome Study Group demonstrated that nearly half the patients were initially admitted for another reason, mainly pain.[47] Pain is the most common presenting syndrome, which makes it difficult to determine whether they are likely to develop acute chest syndrome or not.

1.2.4 Prolonged and Recurrent Painful Episodes:-

Pain is the most frequent presentation at the emergency department for patients with sickle cell disease. It is a marker for severity and a predictor for mortality. One study revealed that there was an increase in painful crises in male patients with hemoglobin levels above 8.5 g/dL (greater than 85 g/L).[48] There are no studies that examine predictor

variables for prolonged painful episodes or other variables that predict recurrent episodes in patients presenting at the emergency department.

1.3.1 Rationale for the Study:-

Sickle cell disease is a complex syndrome that can have progressively poorer adverse outcomes leading ultimately to death if patients are managed poorly in the emergency department. Sickle cell disease patients die early with mean age at death of 5.8 years. Predictors for mortality include dactylitis (RR=2.6), hemoglobin less than 7 g/dl (RR=2.5), and leukocytosis (RR=1.8). Previous CVA or TIA, and history of acute chest syndrome are the strongest predictors of CVA. None of the previous studies focused on emergency department patients. The variables included in the model did not reflect the follow-up time until the patient developed the adverse outcomes. A better predictive model is needed to reflect the emergency presentations and the variables included should reflect the time until the patient develops adverse outcome. Prevention of these adverse outcomes is the ultimate goal of the clinician. To better prevent these adverse outcomes, a better understanding of the presentation of the disease and predictors of adverse outcomes is crucial. However, the current state of knowledge about the disease in the context of the emergency department is very limited. The goal of the current study was to improve upon this knowledge gap.

CHAPTER 2: GOALS AND OBJECTIVES

2.1 Overall Goal: Our overall goal was to develop a better understanding of the clinical features and presentation; historical, clinical examination and laboratory variables; among patients with sickle cell disease in the emergency department and to determine the risk factors for short-term adverse events in order to contribute to future management strategies. We accomplished this by conducting a prospective cohort study in the emergency department.

2.2 Specific objectives: The specific objectives of the study were the following:

1. To describe the clinical presentation of patients presenting at the emergency department with sickle cell disease. This includes their symptoms and related physical signs. It also includes various laboratory parameters.
2. To describe the proportion of patients with adverse outcomes and describe their historical features and physical examination findings
3. To characterize the association between patient characteristics and the short term adverse outcomes for clinically significant outcomes
4. To characterize the association between patient characteristics and the short term adverse outcomes for acute chest syndrome
5. To use multivariate techniques to determine the clinical predictors of clinically significant outcomes and acute chest syndrome.
6. To establish baseline values for hematological parameters in sickle cell disease patients at the study site. These include hemoglobin, leukocyte count, platelets count, and reticulocyte count.

7. To establish baseline values for blood pressure, heart rate, respiratory rate and oxygen saturation in these patients.
8. To establish a database for the various clinical features and laboratory values for future studies for sickle cell disease patients.

Chapter 3: Methods

We conducted a prospective cohort study of patients at the emergency department of a large tertiary hospital. The study population included a cohort of sickle cell disease patients presenting during the study period. We collected various clinical and laboratory predictor variables, which we used to establish the predictors for repeat emergency visits or adverse outcomes after discharge from the emergency department. We collected the data prospectively using a piloted data collection sheet and followed the patients prospectively using a structured telephone follow-up and review of emergency follow-up visits and review of hospital admissions. We entered the data in a previously designed database and analyzed the data using SAS software (SAS Institute Inc, Cary, NC).

3.1 Study Design:-

This was a prospective analytic cohort study conducted at a large emergency department in Muscat (Oman). Patients who did not develop adverse outcomes were compared with those who developed adverse outcomes. The unit of analysis was patients with sickle cell disease who were seen in the emergency department. The outcome measure was short-term adverse outcomes. Because the emergency department visit and all the predictor variables preceded the outcomes in all cases, it was possible to suggest a true association between the predictor variables and the outcomes.

3.2 Study Period:-

The study was conducted during 6 months, from January 1, 2007 until July 15, 2007. The study was interrupted for 2 weeks between June 3, 2007 and June 17, 2007 owing to unexpected emergency weather conditions that caused damage to communications at the study site.

3.3 Setting:-

The study was conducted at the emergency department of the Sultan Qaboos University Hospital in Muscat-Oman. Sultan Qaboos University Hospital is a tertiary teaching hospital with 55 000 emergency department visits each year. All age groups are seen in this emergency department. The emergency department is staffed with 12 emergency specialists as well as rotating emergency residents. There are 3600 visits related to sickle cell disease each year at this emergency department. The study was approved by the emergency department at Sultan Qaboos University Hospital. Ethics approval was obtained from the ethics review board at the study site and by the Ottawa Hospital Research Ethics Board.

3.4 Study Population

3.4.1 Inclusion Criteria:-

All patients with "complaints related to sickle cell disease" who presented to the emergency department were eligible A sickle-cell–related complaint included all clinical presentations caused by sickle cell disease status. This included clinical features which are considered to be more serious in such patients due to the fact that sickle cell disease patients are immunocompromised (e.g. fever). Sickle cell disease is a multi-organ disease and can present with diverse symptoms and signs. The following signs and symptoms are caused directly by sickle cell disease status: pain, acute chest syndrome, anemia, hyperhemolytic crisis, meningitis, bacteremia, pneumonia, arthritis, leg ulcers, priapism, myocardial infarction, acute hepatitis, acute cholecystitis, splenic sequestration, and CVA. Fever is a typical example of a potential for an adverse outcome that is not caused directly by being a sickle cell disease patient. Patient eligibility as a "sickle-cell–

related complaint" case was determined by the emergency department physician and based on the patient having any of the above-mentioned presentations; the following inclusion criteria at the time of arrival to the emergency department were used as well:

1. All age groups were included.
2. Capable of providing verbal consent – or had an available substitute decision maker capable of providing verbal consent.
3. Patients had the initial clinical assessment done by the emergency department physicians.

3.4.2 Exclusion Criteria:-

A patient with any one of the following characteristic was excluded:

1. Clinical problems not related to sickle cell disease and without the potential for adverse outcomes, including pregnancy-related problems, traumatic injuries, allergic reactions, eye-related emergencies such as glaucoma, ear infections, diabetes, and gastrointestinal bleeding.
2. Unable to complete a telephone interview in Arabic or English.
3. Did not have a telephone or who were otherwise unavailable for follow-up 2 weeks after discharge.
4. Unable to give verbal consent.
5. Patients already enrolled within the last 2 weeks. The subsequent visits within 2 weeks of the index visit were considered to verify the outcome.

3.5 Sampling Method:-

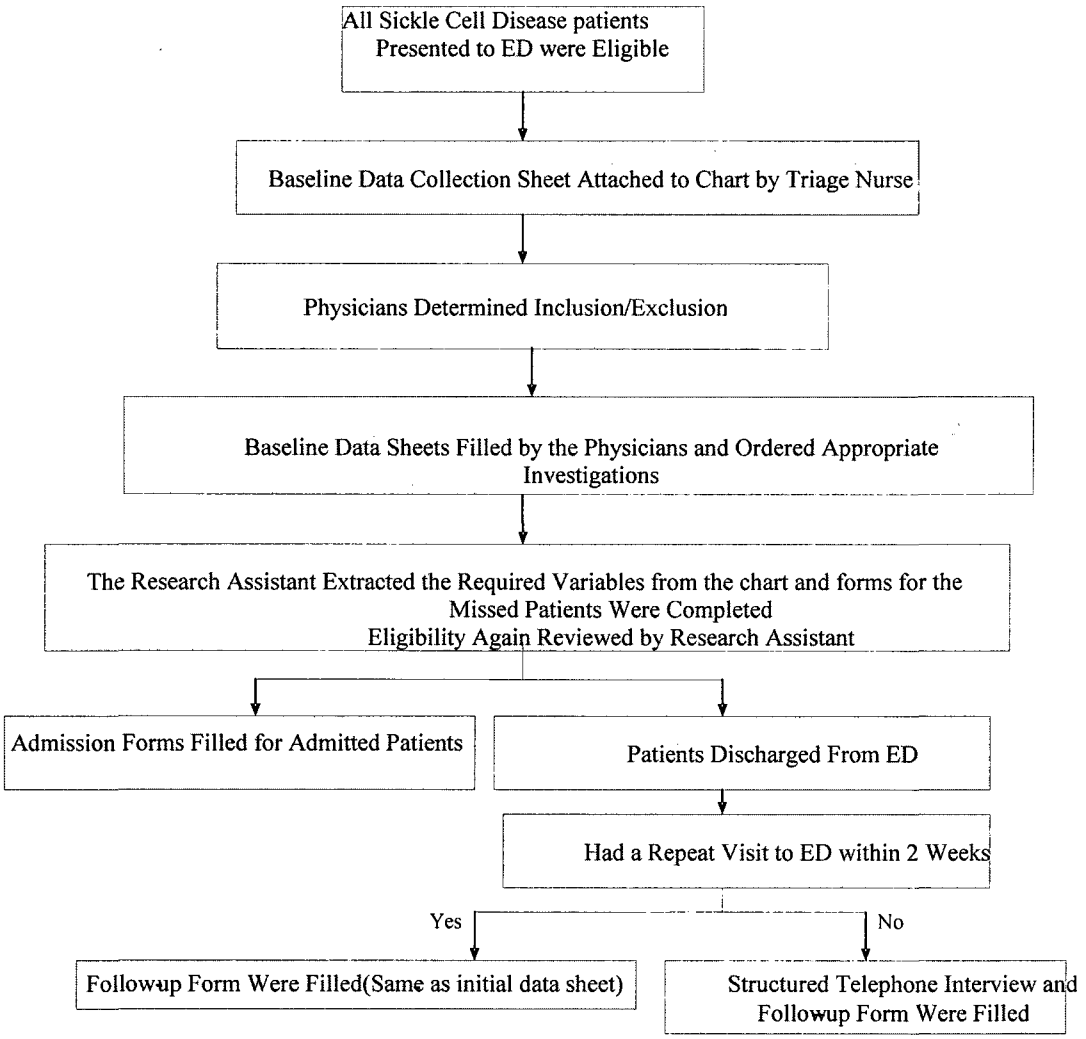
We conducted the study 24 hours a day, 7 days a week. All potentially eligible patients had a data collection sheet attached to the emergency chart by the triage nurse. The initial data collection sheets were filled by the triage nurse and the attending emergency department physicians and because randomization was not needed, a consecutive sampling method; all consecutive patients were included; was used. Forms were later reviewed by the research assistant for eligibility, and those patients who did not meet the inclusion criteria were excluded. A log of all patients with sickle cell disease was made.

3.6 Recruitment Strategies:-

The on-duty clinical triage nurse approached the patients once they had been registered. All patients with sickle cell disease seen in the emergency department and who were alert and capable of providing verbal consent were enrolled if they met the eligibility criteria (See Appendix C for the verbal consent structure). The physicians were responsible for including the patients in the study. The triage nurse and the physicians explained the study objectives and follow-up procedures to the patient (or their substitute decision maker), and the benefits of the study in terms of knowledge gained were explained. We obtained verbal consent for the follow-up phone call. There were no physical risks to the patient, and only the potential inconvenience was a 5- to 10-minute follow-up phone call. All patients (or their substitute decision makers) who consented verbally to participate in the study had baseline data collected (see appendix C for the baseline data collection form). Each patient was asked to provide 2 telephone numbers (their home and a mobile number) and 3 times during the day when they preferred to be

called. A unique serial number for each patient was used on all the forms belonging to that patient so that the different forms could be matched. The variables collected were part of the routine clinical assessment. The flow chart below illustrates the study flow process.

The Study Flow Chart



3.7 Standardized Patient Assessment

3.7.1 Patient Assessment:-

All patient assessments were made by emergency department physicians or emergency residents. Interns and residents enrolled eligible patients but were asked to discuss their assessment with the emergency department physicians as per protocol. We did not measure reliability among the assessors. The physician assessors were trained by means of a 1-hour lecture and by a practical demonstration of how to assess the clinical variables in a uniform manner and how to complete the data collection sheets. The physical examination variables were collected according to the standard clinical assessment performed on each patient.

The physicians recorded their findings on data collection sheets after assessing the patients before discharge or admission. Both negative and positive findings were recorded as per the standard data collection form. Physicians initially assessed the patients shortly after their arrival in the emergency department and reassessed the patients while in the emergency department as per standard clinical assessment of such patients. Meanwhile, ongoing assessments for vital signs, pain score as measured on a visual analogue score, analgesia requirements, oxygen saturation, and Glasgow Coma Score (GCS) score were made by the nursing staff at 1- or 2-hour intervals according to the patient's status. There was no preset minimum observation period, but patients could be discharged from the emergency department once they achieved good pain control and were thought not to have reason for readmission as assessed by the emergency department physician.

3.7.2 Quality Assurance:-

The physicians and nurses were regularly reminded to include eligible patients and to complete the data collection sheets. The quality of the patient assessment was judged by the completeness of the data collection forms and by the number of patients enrolled. Monthly feedback was given to the physicians about the study progress and any individual concerns were addressed accordingly. A log for discharged patients was kept to assure follow-up. A similar log for the admitted patients was kept to avoid enrolling the patients within the ineligibility period. The forms were also later reviewed and all ineligible patients were removed. The results of the study were not revealed.

3.7.3 Selection of Variables:-

The variables selected for assessment in the study were chosen by the investigator with the help of content experts, a hematologist, and an emergency department physician. The variables also were based on the literature published regarding long-term outcome predictors for persons with sickle cell disease. These variables were considered useful in predicting short-term outcomes. The inclusion of too many variables in the study would increase the time required of the physician assessors and might have led to decreased compliance. Several variables discussed in the literature were considered not useful or not feasible for this study. The following variables, therefore, were not assessed: race, dizziness, visual complaints, and hearing complaint. Some variables were thought to rarely occur and therefore were not included. Specifically, the results of previous MRI imaging, transcranial ultrasound, and previous insertion of a portacath were not included. The results of previous MRI or transcranial ultrasound might affect the prediction of a cerebrovascular accident. However, we believe that the occurrence of this adverse

outcome is rare and is not likely to change the overall results. Likewise, hearing and eye complaints were unlikely to have potential predictive ability on the short-term adverse outcomes in this study. The variables selected for assessment were historical features, clinical examination, laboratory and radiologic investigations, and treatment received in the emergency department. The variables were coded as "no" or "yes" unless otherwise specified.

The variables from the history included: (a) presenting complaints (details regarding pain, shortness of breath, fever, cough, chest pain, headache, vomiting, diarrhea, lethargy) and (b) medical history and immunization status (CVA, exchange blood transfusion, surgical procedures, splenic sequestration, immunization, regular medication used, and ICU admission). Acute painful episode details were collected as follows: onset, location, and duration. The severity of the episode was assessed using a visual analogue scale from 0 to 10. Response to therapy was assessed with the same scale. The data were collected by the nurse as part of clinical patient assessment.

Variables from the clinical examination included: Table 3 (a) vital signs; (b) the results of a general physical examination including an examination of the head and neck, chest, abdomen, and neurologic examination; specific attention was paid to patient appearance (whether the patient looked well or toxic), jaundice, pallor, and crackles on chest examination, hepatosplenomegaly, priapism, abdominal tenderness, and focal signs of cerebrovascular accidents; and (c) specific local examination (limb examination for ulcers and inflammation).

Variables from the laboratory investigation included: Table 3 (a) a complete blood count including hemoglobin, white cell count, platelet count, and reticulocyte count; (b) electrolyte levels; and (c) a radiologic investigation (chest radiograph).

Variables from treatment included: Table 3 (a) antibiotic use; (b) analgesic use; (c) intravenous fluids use; and (d) use of hydroxyurea.

3.7.4 Physicians' Judgment: The physicians were also asked to answer 3 questions (not to be used as predictor variables) regarding the possibility of having an adverse outcome: (a) the probability of a repeat emergency visit within 2 weeks (as a proportion); (b) the probability of patient developing sepsis defined as above (as a proportion); and (c) the probability of an admission on first encounter (as a proportion). The physicians were asked to estimate the probability on percentage scale, that is, from 0% to 100%.

3.8 Outcome Measures

3.8.1 Primary Outcome:-

The primary outcome measure was "short-term adverse outcome." A short-term adverse outcome is defined as any of the following in patients with sickle cell disease presenting at an emergency department:

1. Death within 2 weeks of the initial presentation for sickle-cell–related problem.
2. Need for emergency exchange blood transfusion.
3. Splenic sequestration (acute illness characterized by an acutely enlarging spleen and hemoglobin level of more than 2 g/dL below the patient's baseline value).[13]
4. Sepsis (defined as 2 of the following criteria: temperature < 36°C or > 38°C, heart rate > 90, respiratory rate > 20 or $PaCO_2$ < 32 mm Hg/h, WBC < 4000 or > 12 000 ×106/L; or band > 10% and a source of infection).

5. Cerebrovascular accidents within 2 weeks of presentation to the emergency department.
6. Acute chest syndrome (defined as a new pulmonary infiltrates on the chest radiograph in combination with fever, chest pain, or respiratory symptoms).[14, 15.]
7. Hemolytic crisis defined as a hemoglobin level of more than 2 g/dL below the patient's baseline value with an appropriately high reticulocyte count.

Data regarding development of acute chest syndrome, sepsis, splenic sequestration, death, and CVAs were ascertained for the admitted patients using inpatient hospital charts. Death and admission to other hospitals for patients discharged from the emergency department who did not have a repeat emergency department visits were ascertained during the telephone interview. The outcome was blindly ascertained. The outcome measured was considered to be of little subjective nature. If there was controversy about the diagnosis (i.e. diagnosis is not clear or more than one probable diagnoses are considered), 2 emergency department physicians reviewed the charts to reach agreement and to decide whether it was an adverse outcome or not. Owing to their potential lethality, we categorized the following as clinically significant outcomes: death, sepsis, CVA, acute chest syndrome, and splenic sequestration and hyperhemolytic crisis. The short-term adverse outcomes were likely to occur within the first 2 weeks of the initial presentation. The mean duration of the painful crisis was 5 days, and another week as a washout period before a new episode was considered. Other adverse outcomes like CVA were likely to present within the first 2 weeks of the acute episode. The outcome measures were blindly and independently adjudicated. The follow-up telephone interview is listed in Appendix E.

3.8.2 Secondary Outcomes:-

We modeled the independent variables to predict the development of acute chest syndrome as a separate outcome. We thought that we could examine this specific outcome separately. The main reason we did this analysis was to explore the variables that could be used to develop a clinical decision rule in the future to predict this potentially lethal diagnosis.

3.9 Data Collection and Management:-

Baseline data were collected while the patient was in the emergency department (see Appendix D for data collection sheet). Outcome data were collected through a structured telephone interview and patient charts (see Appendix E and F for data collection sheet for the admitted patients and the structured telephone interview respectively).The data were collected at different levels. The data collection sheet was attached to the chart as soon as the patient was registered. The triage nurse measured the vital signs and recorded them on the sheet. Measuring the vital signs was part of the triage nurse's protocol. The emergency department physician filled out the physician data form. The laboratory data were extracted from the chart and the electronic records and recorded in the data collection sheet by the research assistant who also reviewed the inpatient hospital records and completed the inpatient form after the patient was discharged. The genetic subtypes of sickle cell disease were ascertained using the hospital database and the patients' charts. The emergency department coordinator was responsible for the database. Data collected for baseline measures included patient complaints, patient demographics, medical history, co-morbidities, the management and course of the disease in the emergency department, and the course of the disease as an in-patient and during follow-up. The details were shown on the data collection sheet. If the

patient had a repeat visit, a follow-up data collection sheet was filled. To simplify the study and avoid missing patients, the follow-up data collection sheet was the same as the baseline data collection sheets. The variables collected were considered as being clinically important in deciding which risk factor could predict a potential adverse outcome. Table 2,3 and 4 shows the variables collected.

The data collection sheet had been previously piloted to ensure that the variables were easily understood and the patients could be recruited successfully. Data collected from the baseline visit and the outcome collection sheets were entered into a Microsoft Excel database developed by the principal investigator. All the patient records were electronically entered and saved. This made referring back to these collection sheets easy and accessible to the research assistant. No patient was admitted to other hospitals and hence no discharge summary from other hospitals was obtained. A case summary for each patient that included the baseline data and follow-up data was created (see Appendix G). The data were kept confidential and in a safe locked room. The principal investigator, the research assistant, and the database manager were the only ones with access to this data. The data was stored at the study site in the emergency department.

3.10 Statistical Analyses

3.10.1 Baseline Characteristics Analysis:-

Using SAS (version 9.1), we prepared descriptive statistics of the baseline characteristics. The various clinical subtypes of sickle cell disease patients and the clinical presentations were reported as proportions. We also reported frequency counts for categorical variables and means and standard deviations for continuous variables.

Range was reported for age. Frequencies of outlying points and stem and leaf plots were examined for baseline characteristics. Original data were used to verify outlier data. A binary variable is more easily understood and more clinically relevant. Hence, we did various analyses to decide the various cutoff points for the continuous variables. Cutoff points, which were clinically sound and statistically significant, were chosen. Clinically important cutoff points were determined by the investigator and discussed during the research group meetings. If more than 1 cutoff point was determined to be equally important on clinical ground, we included the one with the lowest *P* value.

3.10.2 Univariate Analyses:-

The proportion of the adverse outcomes was determined by dividing their occurrence by the number of patients during the study within each group. *P* values were reported for the estimated incidence. Although the same adverse outcome occurs more than once for the same patient, we reported the most clinically relevant adverse outcome. Demographic and historical data as well as the results of clinical examinations and laboratory analyses of patients who developed adverse outcomes were compared with those who did not develop adverse outcomes using the chi-square test or *t* tests where appropriate. Values for *P* less than .05 were considered statistically significant. Those variables making clinical sense and having a *P* value less than .25 were used in subsequent multivariate analyses.

3.10.3 Multivariate Analyses:-

We used multivariate statistical analyses to control for potential confounding and to model the variables to determine the predictors of adverse outcomes. The objective was to find the best combinations of predictor variables to detect short-term adverse

outcomes. We evaluated the strength of the relation of each variable with the outcome using adjusted odds ratios with 95% confidence intervals.

Multiple logistic regression analyses were used for this purpose. We evaluated all the variables for the model. We modeled the continuous variables as categorical to determine the best model. Initial univariate analyses were conducted for each variable and those with *P* values less than 0.25 or of important clinical meaning was included in the model.

Variables were entered using stepwise selection with a *P* value of entry of .25. Those found to be statistically associated with the outcomes had their association reported as odds ratios. Statistical significance of independent variables was assessed using the likelihood ratio test (with a *P* value of $< .05$ as statistically significant). Deviance was used to find the best model. Regression diagnostics examining multicolinearity, linearity, influential data points, and outliers were used. Goodness of fit was measured using the Hosmer-Lemeshow approach.

3.10.4 Subgroup Analysis:-

Patients presenting with fever represented a special group with a greater potential for life-threatening events. Fever is a common presentation. Patients with sickle cell disease are immunocompromised owing to their poor spleen function and consequent potential for developing sepsis and ultimately dying. Historically, it has been difficult to differentiate the patient who might develop sepsis from those who will not develop it. Hence, we did an exploratory analysis to determine if patients with fever have more frequent adverse outcomes and potential predictors for such outcomes. For the purpose of this study, we categorized fever as a temperature of more than 38.0°C.

3.10.5 Sample Size Calculation:-

Calculating sample size for multivariate logistic model is controversial. The sample size in our study was based on the estimated incidence of adverse short term outcome. Because the incidence of repeat emergency visits is known and repeat emergency visits patients are more likely to develop adverse outcomes, our sample size was based on the incidence of repeat emergency visits. The other adverse outcomes are quite rare and would need a very large sample size which will not be feasible in our population setting and time frame. Given what we have known from Sultan Qaboos University Hospital emergency department data base, there were approximately 35% return visits to the emergency department within a 2-week period. We had 72 variables to collect though history, physical examination, laboratory investigations, and follow-up. We discarded 65% of the variables after the univariate analysis which resulted in 25 variables that were evaluated in the LR model. An estimate was that we needed 10 adverse outcomes for every variable in the model, and therefore required 250 such cases required (10X25=250). Therefore, our estimated sample size was 714 (250/0.35=714) emergency visits. Using 25% as a bound on the estimated repeat emergency visits, we estimated the precision of our estimated sample size to be between 570 and950 cases. For the purpose of the thesis, our study ran over a 6-month period. We reached our targeted number during the study period.

3.10.6 Missing Data:-

Frequency reports for the missing data were reviewed and charts and the laboratory database were reviewed to fill in the missing data. Multiple imputation techniques were used to accommodate and account for missing data and to have less

biased estimates for our inference. It uses all the available data with and without missing. This process involves a series of statistical protocols which takes into account the uncertainty of missing data. This process involved 3 distinct phases: the missing data were filled in 5 times to generate 5 complete data sets. We then analyzed the complete data sets using standard statistical analyses. We combined the results from the 5 data sets using the mi-analyze procedure in SAS to produce inferential results. To check the imputation method, we performed a sensitivity analysis removing the variables with the maximum missing observations.

3.11 Ethical Issues:-

The study protocol was reviewed and approved by the institutional ethics review board at Sultan Qaboos University Hospital before data collection (See Appendix H for the ethics approval). The study was also approved by the ethics review board of the Ottawa Hospital (see Appendix I for the ethics approval by the Ottawa Hospital Research Ethics Board). The study was observational and did not have an intervention and therefore, there was no potential patient harm from the study. Because patients were managed using standard care, there were no potential risks to the patients due to the study protocol. Verbal consent was obtained for the telephone follow-up (see Appendix A for the verbal consent structure). The data were kept strictly confidential.

CHAPTER 4: RESULTS

4.1 Study Flow:-

A total of 1046 eligible patients were identified during the 6-month study. The study flow is illustrated in Figure 2. Two hundred thirty-nine patients were excluded because they visited the emergency department more than once within 2 weeks. Fifteen patients were excluded because there were pregnant and likely to be admitted to the hospital for other reasons. In total 20 patients were missed with 17 patients not enrolled in the study and no data collection form was filled in and 3 patients were admitted to the hospital, but there were no data collection sheets for the emergency visit. Fifteen patients refused to participate. Twenty five patients were lost to follow-up because of unexpected weather conditions during June of whom none were identified as having significant adverse outcome using the hospital database.

4.2 Descriptive Statistics

4.2.1 Descriptive statistics for the Cohort:-

Data from 732 patients were evaluated and used for descriptive statistics that included demographic features, medical history, and results of clinical examinations and laboratory studies. The mean age of the patients was 20.4 years. Women comprised 39.2% of the study population. The patients' demographics and presenting problems are summarized in Table 5. The vast majority of patients presented with pain: 49% had frequent painful episodes (defined as more than 2 episodes per month). Regular oral penicillin was used in 76.8% of the cohort, while hydroxyurea was used by 30.3% of the patients. The clinical examination and laboratory features are summarized in Table 6. The patients' mean temperature was 36.9°C, and the mean oxygen saturation was 98.9%.

Regarding appearance, 40.9% of the patients appeared well, while 2.3% appeared sick or toxic. Overall, 79.5% of the patients received intravenous fluids as part of treatment in the emergency department. The mean white cell count was 12.21 × 10^9/L and the hemoglobin was 9.8 g/dL. The mean reticulocyte count was 7.6%.

Three hundred fourteen patients were excluded. The patients' characteristics of those patients are summarized in Table 7. The mean age of the patients was 21.0 years. Women comprised 42.0 % of the excluded patients. The vast majority of patients presented with pain (87.6%) while minority presented with fever (7.0%). The patients' mean temperature was 36.9°C, and the mean oxygen saturation was 99.0%. Overall, 70.4% of the patients received intravenous fluids while 3.8% received intravenous antibiotics as part of treatment in the emergency department. The mean white cell count was 11.2 × 10^9/L and the hemoglobin was 10.2 g/dL. The mean reticulocyte count was 8.3%.

The cohort was evaluated for various outcomes (Table 8). Three hundred eight patients (42.1%) were admitted to the hospital; 52.7% had a repeat emergency department visit within 2 weeks of their initial presentation. Seventy-five patients (10.2%) developed a clinically significant outcome. Forty-two patients (5.7%) developed acute chest syndrome.

4.2.2 Descriptive Statistics for the Admitted Patients and Telephone Follow-up Patients:-

Table 9 demonstrates the clinical and laboratory characteristics of the patients with sickle cell disease who were admitted and patients requiring telephone follow-up within 2 weeks of emergency department presentation. Three hundred eight patients

(mean age, 19.34 years; women, 40.3%) were admitted to the hospital. Of the admitted patients, 16.2% received antibiotics; 84.7% were treated with intravenous narcotics. One patient died in the hospital. This patient had numerous prior emergency department visits. On the day of admission, he went to bed and could not be subsequently aroused. A computed tomography scan hospital showed an intraventricular hemorrhage. The patient died 4 days after admission.

One hundred fifty-two patients had a follow-up telephone call 2 weeks after their index emergency visit. One patient died at home 5 days after his emergency department visit for a painful episode. At the time of his discharge from the emergency department, he had been doing well and was asymptomatic. The cause of his death remains unclear.

4.2.3 Baseline Vital Signs and Laboratory Parameters in the Sickle Cell Disease Cohort:-

Table 10 shows the various baseline parameters for the cohort. We analyzed the different parameters according to age. Little physiological changes occur after the age of 8 years; hence we categorized the results accordingly. We found that 8 years of age, was the most appropriate cut off value using statistical testing ($P < 0.05$) for those parameters which differ by age. Those parameters that were statistically different in the different age groups are presented separately within that age group. Those parameters that were not statistically different were not presented within different age groups. The mean oxygen saturation was 98.8%. The mean temperature was 36.7°C. As expected, the mean blood pressure tended to be higher as age increased. The mean values still fall within the expected normal range for persons in the general population. The mean hemoglobin level

tended to be lower in younger patients (those under 8 years) and their reticulocyte levels tended to be higher. This difference was statistically significant.

4.3 Univariate Analysis for Clinically Significant Outcomes:-

We defined clinically significant outcomes as death, acute chest syndrome, splenic sequestration crisis, sepsis, hyperhemolytic crisis, CVAs, and emergency exchanged transfusion. We divided the cohort into those patients who did and did not have clinically significant outcomes. We did the analysis of continuous variables using different cutoff points. A binary variable is more easily understood and more clinically relevant. Hence, we did various analyses to decide the various cutoff points for each of the continuous variables. We decided on the best cutoff point using clinical importance and statistical significance. When more than 1 cutoff point was found to be equally useful on clinical ground, we included the values with the smallest *P* value. The cutoff point of 96% oxygen saturation was found and used. A cutoff point of 15% for the reticulocyte count was found and used. The following cutoff points were found to be the best cutoff points for the continuous variables: age less than 8 years; temperature, 38°C; heart rate, 100; oxygen saturation, 96%.

Table 11 shows the results of the univariate analyses of the historical features. The patients who developed clinically significant outcomes were more likely to be younger than 8 years (17.3% vs 5.8%; $P < 0.001$). They were more likely to present with fever (20.0% vs 9.7%; $P < 0.001$). They were also more likely to have a prolonged painful episode (50.7% vs 16.9%, $P < 0.001$) and to have had previous blood transfusions (32.0% vs 15.8%, $P < 0.001$). They were less likely to have history of splenectomy (4.0% vs 13.9%, $P = 0.01$) and less likely to be on regular codeine (45.3%

vs 63.6%; $P = 0.002$). Other statistically significant findings included history of chest pain and history of splenic sequestration crisis.

The results of univariate analyses are given in Tables 12 and 13 for the examination findings done in the emergency department and the results of laboratory analyses. Patients with clinically significant findings were more likely to be tachycardic, defined as having a heart rate greater than 100 (38.7% vs 17.0%; $P < 0.001$). They were more likely to have oxygen saturation values less than 96% (18.7% vs 6.2%; $P < 0.001$). They were likely to appear toxic (9.3% vs 1.5%; $P < 0.001$). Other variables found to be statistically significant were respiratory rate greater than 24 (16.0% vs 7.3%), temperature > 38.0°C (10.7% vs 5.2%), pain visual analogue score > 8.0 (8.0% vs 3.5%), pallor appearance (61.3% vs 30.9%), and having chest crackles (14.7% vs 1.5%). Patients with clinically significant findings were likely to have hemoglobin<7g/dl (18.7% vs 1.2%; $P < 0.001$). They were more likely to have reticulocyte>15% (18.7% vs 2.3%; $P < 0.001$).

4.4 Multivariate Data analysis for Clinically Significant Outcomes

4.4.1 Model Building Process:-

All possible predictor variables were analyzed with univariate analyses. For the laboratory features, 51% of the patients underwent laboratory investigations. We performed multiple imputations to do the analyses on the completed data set. Using listwise deletion would lead to more-biased results and a loss of a significant amount of data. All the predictor variables used a multiple imputation technique. The laboratory features with missing values were imputed using **mi** syntax in SAS. This resulted in 5 different but similar data sets (taking into account the uncertainty of the missing values).

Then we did a stepwise logistic regression on the various data sets. This logistic regression analysis was done at a value for *P* of 0.25 and *P* value to remove of 0 .05. Forty-one variables of *P* value less than 0.25 were offered to a model. The results of the stepwise logistic aggression were combined using **mianalyze** syntax in SAS. This yielded the final logistic regression model.

4.4.2 Interaction Terms for the Logistic Regression Model:-

We did not add interaction terms to the model as per study protocol.

4.4.3 Goodness-of-fit for Logistic Regression Model:-

The Hosmer and Lemeshow test for goodness-of-fit was performed. We did the analysis for the various imputed values, which showed there is no evidence of a lack of fit (*P* =0 .87). Removing the variable with the least significant *P* value (splenectomy) resulted in a more refined model (one less variable) without changing the R^2 significantly (decreased from 31.7 to 30.5).

4.4.4 Final Logistic Regression Model:-

Our final model is shown in Table 14. The following variables were included: a prolonged painful episode (OR 10.1; 95%CI 5.3-19.3), age less than 8 years (OR 2.4; 95%CI 1.001 -5.9), oxygen saturation less than 96% (OR 3.9; 95%CI 1.6-10.9), patient appearing toxic (OR 7.8; 95%CI 2.2-27.2), presence of chest crackles (OR 6.5; 95%CI 2.3-18.6), splenomegaly (OR 2.6; 95%CI 1.2-5.5), local limb tenderness (OR 0.2; 95%CI 0.08-0.7), hemoglobin less than 7 g/dL (OR 3.6; 95%CI 1.11-11.6), reticulocyte count more than 15% (OR 4.0; 95%CI 1.4-11.5). The coefficient estimates are included in Table 15.

4.5 Univariate Analysis for Acute Chest Syndrome:-

As for the analysis of the clinically significant outcomes, the analysis of continuous variables was performed using different cutoff points. When more than 1 cutoff point was found to be clinically useful, we included the values with the smallest *P* value. The cutoff point of 92% oxygen saturation was found and used. A cutoff point of 15% for the reticulocyte count was found and used. The following cutoff points were found to be the best cutoff points for the continuous variables: age, 8 years; temperature, 38°C; heart rate, 110; white blood cell count, > 12×10^9/L; hemoglobin, greater than 7 g/dL.

Table 15 shows the results of univariate analyses from the historiy variables. There were 42 positive cases for acute chest syndrome in the cohort. Patients who developed acute chest syndrome were less likely to be women (23.8% vs 40.1%; *P* <0 .03). They were more likely to present with fever (28.6% vs 9.7%; *P* <0 .03). They were also more likely to have a prolonged painful episode (50.7% vs 16.9%; *P* <0 .001) and to have previous blood transfusions (28.6% vs 16.8%; *P* <0 .05). They more frequently had cough (28.6% vs 5.9%; *P* <0 .001) and chest pain (35.7% vs 9.7%; *P* <0 .001), and they were less likely to have history of splenectomy (2.0% vs 13.5%; *P* = 0.04).

Tables 16 and 17 shows the results of univariate analyses for the examination findings done in the emergency department and the laboratory features. Patients with clinically significant findings were more likely to be febrile (14.3% vs 5.2; *P* = 0.01), defined as temperature 38°C. They were also more likely to have an oxygen saturation value less than 92% (7.1% vs 0.4%; *P* =0.003). They were more likely to appear toxic (7.1% vs 2.0%; *P* <0 .03) and have a higher pain visual analogue score defined as score

greater than 8 (11.9% vs 3.5%; P <0 .001). Clinical findings of chest crackles also were higher in the acute chest syndrome group (23.8% vs 1.6%; P <0 .001). Other statistically significant variables in the acute chest syndrome group were heart rate above 110 (31.0% vs 18.6%), white blood cell count greater than 12×10^9/L (42.9% vs 19.1%), and reticulocyte count greater than 15% (11.9% vs 3.5%). Patients with acute chest syndrome were likely to have white blood cell count>12 (42.9% vs 19.1%; P <0 .001). They were more likely to have reticulocyte>15% (11.9% vs 3.5%; P =0 .02).

4.5 Multivariate Analysis for Acute Chest Syndrome

4.6.1 Model Building Process:-

As for the clinically significant outcome model building process, we used a multiple imputation technique to input the missing values of the laboratory variables. We performed a stepwise logistic aggression on the various data sets. This stepwise logistic regression analysis was conducted with a P value to enter of 0.25 and P value to remove of 0.05. Thirty-four variables with a P value less than 0.25 were offered to a model. The results of the stepwise logistic aggression were combined using mianalyze syntax in SAS. This yielded the final logistic regression model.

4.6.2 Goodness-of-fit for Logistic Regression Model:-

The Hosmer and Lemeshow test for goodness-of-fit was performed. The analysis of the imputed data, showed there was no evidence of a lack of fit (P = 0.54). Removing 2 variables with the least significant P values (regular use of penicillin and WBC > 12×10^9/L) resulted in a more refined model (2 less variables) without changing the R^2 significantly (increased from 36.2 to 36.3).

4.6.3 Final Logistic Regression Model:-

Our final model is shown in Table 18. The following variables were included: a prolonged painful episode (OR 22.0; 95%CI 8.7-55.3), oxygen saturation less than 92% (OR 17.7; 95%CI 1.7-184.9), history of cough (OR 4.5; 95%CI 1.7-12.0), history of pneumococcal vaccine (OR 0.33; 95%CI 0.11-0.98), presence of chest crackles (OR 9.5; 95%CI 2.6-34.7), local limb tenderness (OR 0.20; 95%CI 0.05-0.80), and reticulocyte count more than 15% (OR 4.9; 95%CI 1.2-19.7). The coefficient estimates, and their corresponding odds ratios with their 95% confidence intervals are included in Table 19. A prolonged painful episode was the strongest predictor variable (OR=22.0) for acute chest syndrome followed by low oxygen saturation. The standard error was high for the low oxygen saturation owing to a low prevalence in this group. However, we felt that this is a clinically important variable and so, we kept it in the model.

4.7 Subgroup Analysis: Patients with Fever:-

We performed a subgroup analysis for patients with fever to see if they were likely to develop adverse outcomes. Table 19 shows that patients with fever were likely to be admitted to the hospital, likely to develop clinically significant outcome, and likely to acute chest syndrome. Temperature is not a predictor in the multivariate model probably because other variables were more likely to predict the outcome variable.

4.8 Sensitivity and Specificity of the Logistic Regression Model

4.8.1 Sensitivity of the Model for Clinically Significant Outcome:-

Sensitivity and specificity of the regression model for clinically significant outcomes was determined using probability classification cutoff points from 0.003 to 0.95. The sensitivities and specificities for this range of cutoff points are illustrated in

Table 20 and their corresponding plot is illustrated in Figure 3. The receiver operator characteristic curve (ROC) for the final logistic regression model is illustrated in Figure 4. The area under the curve was 0.88. This indicates that the model has excellent ability to discriminate between those subjects who experienced clinically significant outcomes and those who did not.

4.8.2 Sensitivity of the Model for Acute Chest Syndrome:-

Sensitivity and specificity of the regression model for clinically significant outcomes was determined using probability classification cutoff points from 0.02 to 0.95. The sensitivities and specificities for this range of cutoff points are illustrated in Table 21 and their corresponding plot is illustrated in Figure 5. The ROC for the final logistic regression model is illustrated in Figure 6. The area under the curve was 0.88. This indicates that the model has excellent ability to discriminate between those subjects who experienced acute chest syndrome and those who did not.

4.9 Physicians Judgment:-

We asked the physicians 2 questions. The first was to estimate the admission probability on a scale from 0 to 100% for the patients on their first encounter. The response in answering this question among the physicians was 39.1%. We found that patients were more likely to be admitted if the physicians estimated their admission probability as 40% or more (42.3% versus 12.2%). The area under the ROC curve for the physicians' judgment is 0.65. This demonstrates that the physicians are at best fair in accurately predicting hospital admission. The patients were less likely to be admitted if the physicians estimated their admission probability to be 20% or less (45.4% versus 15.4%). The area under the ROC curve for the physicians' judgment is 0.65. This also

demonstrates that physicians are at best having a fair probability in predicting which patients are to be less likely admitted to the hospital. The second question was to estimate the chance of repeat emergency department visits within 2 weeks. The response to this question was only 6.5%, and hence the results were not analyzed further.

CHAPTER 5: DISCUSSION

We successfully enrolled a consecutive sample of 732 sickle cell disease patients over the six month study period. Overall, the study population was young. Most of the patients presented with painful crisis. There were 75 cases (10.2%) with clinically significant adverse outcomes and 42 cases with acute chest syndrome. The variables that were found to be statistically significant in the multivariate analysis to predict clinically significant outcomes included: age less than 8 years old, prolonged painful episode, oxygen saturation less than 96%, patients appearing toxic, chest crackles, splenomegaly, hemoglobin less than 7 g/dl and reticulocytes more than 15% and presence of local limb tenderness. Patients with acute chest syndrome were more likely to have: prolonged painful episode, oxygen saturation less than 92%, history of cough, chest crackles, reticulocytes more than 15%, local limb tenderness and received pneumococcal vaccination. In general, the younger the patient and the sicker they were, the more likely they were to develop adverse outcomes.

5.1 Study Enrolment:-

We enrolled 732 patients during the six-month study period. There were 75 cases of clinically significant outcomes. On average, there were 12.5 cases per month. We conducted the study over a six month period. However, we were unable to achieve a complete follow-up on 25 patients who were initially enrolled. The main reason for this incomplete follow-up was exceptional weather conditions causing floods and damage to the infrastructure. In an effort to verify if these patients had any adverse outcome, we searched our hospital database, but did not find these patients having adverse outcome. If those patients developed adverse outcomes and have some variables common, our results

might have been biased by not identifying important predictor variables. Nevertheless, we will continue to try to find out if these patients developed any adverse outcomes, as this event happened toward the end of our recruitment period. To improve follow-up in future studies, we will include the mailing address to ensure that patients who cannot be reached by phone can be contacted using mail.

We consider our study to be a success because it is the first prospective study conducted in the emergency department that looked specifically at the short term outcome. This was also the first prospective study conducted at the emergency department at the study site. We were able to achieve this by providing continuous reminders to the emergency department staff about the importance of the success of this study as it opens the door to future research. There were no financial incentives to the patients or the staff in conducting this study and we did not receive any funding from external sources. The cost was absorbed by the department clinical fund.

5.2 Clinical Presentation of Sickle Cell Disease to the Emergency Department (Objective 1):-

One goal of the study was to describe the clinical presentation of sickle cell disease to the emergency department. We chose this group of patients because they are at high risk of developing adverse outcomes. They are at high of risk of death, sepsis and other severe outcomes.[14] We were particularly concerned about the emergency management of these patients and what could predict the adverse outcomes or make the diagnosis of these outcomes easier.

We successfully enrolled a consecutive sample of 732 patients over the six month study period. Overall, the study population was young; with mean age of 20.4 years. This

reflects the mean age of the general population at the study site, where 33.8% of the population is below 15 years (2003 census-Oman). The most common presenting problem was painful crisis found in 92% of the clinical presentations. Limb pain was the most common site for the painful crisis, amounting for 36.5% of the complaints, followed by back pain, causing 24.5% of the presenting complaints. Chest pain led to 11.2% of the clinical presentations. Almost half of the patients had frequent painful episodes defined as more than 2 episodes per month. Gill et al. reported painful episodes as the most common presentation during childhood.[15]

Our results are unique to the emergency department, in that there are no studies to our knowledge that have looked at the clinical presentation in the emergency department. The reported rate of pain was much lower in the previous prospective study. Their reported average rate was 0.8 episodes per patient-year in sickle cell anemia.[12] Although we did not report the rate, we believe that it will be much higher, as 49.0% of our patients reported more than two episodes per month. This could be due to multiple factors, including genetic and environmental factors. Dehydration was postulated to precipitate a painful crisis. We found no evidence in our study or in published literature to support this belief. The mean pain numeric score was 5.7, with 72% of patients having a score of 5 or more, which indicates that patients with moderate to severe pain are likely to present to the emergency department.

In addition, we were surprised to find that 76.8% of our cohort is using regular penicillin to prevent serious bacterial infection. The evidence available reveals that using regular penicillin is indicated up to the age of five years, beyond which its use is controversial.[28] We were also surprised that only 79.5% of the patients had received IV

fluid, despite the fact that 92% presented with pain. One possible explanation for this difference is the practice variation between the physicians. It is also unclear whether routinely giving extra fluids to people with sickle cell painful crisis, but without dehydration, will be beneficial or harmful.[49]

5.3 Proportion of Patients with Adverse Events (Objective 2):-

This is the first study that has described adverse outcomes in patients who presented to the emergency department. The admission rate was 42.1% and severe painful episodes (79.2%) not responding to the emergency management were the most common reason for admission. Intravenous narcotics were prescribed to 84.7%, while intravenous antibiotics were prescribed in 16.2% of the admitted patients. One patient died during the hospital admission. We believe that the most common reason for the high admission rate was that the physicians were reluctant to prescribe appropriate doses of outpatient narcotics. Most of hospital admissions would probably be avoided if the patients had good pain control as outpatients. This is evident from the type of the narcotic being prescribed, which is codeine and it was prescribed 61.7% of the time.

Codeine is known to be a poor analgesic if compared to morphine and is not superior to acetaminophen. A recent study concluded that there was no significant difference between patients receiving codeine or acetaminophen in the change in pain score for any time period, or in the number of patients achieving adequate analgesia.[50] Another study which is evaluating codeine as analgesia in patients with sickle cell disease is currently recruiting patients.

A large proportion of patients (32.6%) had repeat emergency visits within two weeks of their initial visits, with the most common reason being pain. One study found

the admission rate to be as high as 64%, and the reason for admission was inadequately controlled painful crisis in the emergency department.[51] A daycare approach in the management of the sickle cell disease patient could be an ideal solution to avoid such a high admission rate. A retrospective study concluded that a dedicated day hospital facility has the potential to provide efficient and timely management of uncomplicated painful vaso-occlusive crisis through reduction of length of stay.[52,53] This is an attractive idea in the study center setting to reduce the load on the emergency department and in hospital admitting services, while providing optimal care for those patients.

There were 75 cases (10.2%) with clinically significant adverse outcomes. The death occurrence was too uncommon to allow a separate subgroup analysis being performed. Two patients died during the study periods. Both patients were brothers. The first patient died unexpectedly at home. Although he was well on the day he died, he was found dead in his bed. There was no autopsy conducted. There is a suspicion that his death could be attributed to narcotic overdose because he had experienced previous episodes of apnea while admitted, which was attributed to overdose. This patient also had very frequent painful episodes. His brother was complaining of moderate headache before going to bed. He could not be awakened and was brought to the emergency department. After being intubated, a CT scan of the head showed severe intraventricular hemorrhage and he died in the intensive care unit (ICU) few days later. He also had very frequent painful episodes. We do not believe that the death of those brothers would have been prevented by a change in the course of their management.

Finally, the most common significant adverse outcome was acute chest syndrome. There were 42 (5.7%) cases of acute chest syndrome, followed by splenic sequestration

crisis (13 cases), sepsis (8 cases), hyperhemolytic crisis (6 cases), exchange blood transfusion (3 cases), and CVA (1 case). A separate discussion of the clinically significant outcomes of acute chest syndrome is to follow.

5.4 The Association between Patient Characteristics and the Clinically Significant Outcomes (Objective 3):-

There are a number of variables associated with clinically significant outcomes. There were a total of 75 positive cases that developed clinically significant outcomes. A total of 26 variables from history, physical examination, and laboratory features had a p-value of 0.05 or less in the univariate analysis. The patients who developed clinically significant outcomes were more likely to be younger, present with fever, have a prolonged painful episode, received blood transfusions, have chest pain, and have a history of splenic sequestration crisis. For these patients, clinically significant findings were more likely to be tachycardia, oxygen saturation of less than 96%, more likely to appear toxic, respiratory rate >24, temperature >38.0, pain numeric score >8.0, and chest crackles. They were more likely to have wbc >12, hb <7g/dl, had reticulocytes >15%. These results reflect the clinical nature of any disease. The patients who have more severe disease are more likely to develop adverse outcomes. Fever and prolonged painful episodes support this explanation. They also have significant past history as they are more likely to have received blood transfusion and had splenic sequestration. Their vital signs and clinical examination also supports that they are likely to develop adverse outcomes. They are tachycardic, have more severe pain, less oxygen saturation, and appear toxic. Their laboratory parameters also support that they are sicker patients. They have higher wbc, lower haemoglobin and higher reticulocytes count.

We were surprised that treatment with hydroxyurea does not seem to protect patients from developing adverse outcomes. This is contradictory to the available evidence from randomized controlled trials. Studies concluded that hydroxyurea is efficacious in children and adults with SCD; with an increase in Hb F%, and reduction in hospitalizations and pain crises. Another randomized controlled trial found no significant difference between hydroxyurea and placebo in stroke (RR 0.64, 95% CI 0.11 to 3.80), hepatic sequestration (RR 0.32, 95% CI 0.03 to 3.06), or in mortality related to sickle cell disease (RR 0.48, 95% CI 0.09 to 2.60).[54] However, few studies have measured the effectiveness of hydroxyurea for SCD in usual practice.[33, 55] Our study is observational and intended to be pragmatic in nature and hence the effectiveness of hydroxyurea could be examined in usual clinical practice. Hydroxyurea is only used in 30.3% of the cohort, despite the fact that half of our patients had very frequent painful episodes. Another possible explanation for our findings is non-compliance with the prescribed treatment especially it is a lifelong treatment. Our results should be replicated in other effectiveness studies before reaching any conclusion regarding its use.

5.5 The Association between Patient Characteristics and the Acute Chest Syndrome (Objective 4):-

The acute chest syndrome (ACS) in sickle cell disease is currently defined as a new infiltrate on chest radiograph associated with one or more symptoms, such as fever, cough, sputum production, tachypnea, dyspnea, or new-onset hypoxia.[52] There were 42 (5.7%) cases that developed acute chest syndrome during the study period, making it the most common clinically significant complication. A similar rate was reported in the

CSSCD study.[24] Most of the patients (79%) in our study developed acute chest syndrome after admission to the hospital. CSSCD study reported 48% of the episodes, acute chest syndrome developed during hospitalization for acute pain or other causes. This indicates that a large proportion of patients with acute chest syndrome develop it a few days after the initial presentation. It may seem obvious that the pathophysiological process takes time to lead to the clinical diagnosis of acute chest syndrome.

Chest pain, fever, cough were the most common complains. Temperature>38.0, tachycardia, severe pain, pallor, and chest crackles were the most common physical findings. A total of 20 variables from history, physical examination; and laboratory features had a p-value of 0.05 or less in the univariate analysis. The patients who developed acute chest syndrome were more likely to be male, present with fever, had a prolonged painful episode, complained of shortness of breath, cough, and chest pain, and had a history of blood transfusion as well as a history of splenectomy. The clinically significant findings for these patients were more likely to be febrile, tachycardia, have oxygen saturation less than 92%, less likely to appear well, more likely to appear toxic, had pain numeric score > 8.0, and had chest crackles. They were more likely to have wbc >12 and higher reticulocytes count. These variables are similar to the variables which predict clinically significant outcomes. This was not a surprise, because acute chest syndrome is the most common clinically significant outcome. We noticed again that the patients who have more severe disease are more likely to develop acute chest syndrome. A Saudi study reported similar findings and found that fever, cough, and chest pain were the most common symptoms. Raised temperature, tachypnea and tachycardia were the most common findings.[56]

5.6 Multivariate Analysis to Determine the Clinical Predictors for Clinically Significant Outcomes (Objective 5):-

Variables found to have a p-value of < 0.25 were simultaneously evaluated using logistic regression. Variables with a p-value of 0.05 or less were kept in the final model if they clinically important. The following variables were found to be statistically significant and therefore were kept in the final logistic regression model: age less than 8 years old, prolonged painful episode, oxygen saturation less than 96%, patients appearing toxic, chest crackles, splenomegaly, hemoglobin less than 7 g/dl and reticulocytes more than 15%. One variable was found to decrease the chance of developing adverse outcomes, namely, presence of local limb tenderness. All the variables were thought to be clinically relevant and therefore kept in the model.

A prolonged painful episode had an OR=10.1 (95% CI, 5.3-19.3). This result was surprising to us. Patients who have a prolonged painful episodes are more likely to have a severe episode and more likely to develop significant adverse outcomes. This could be due to the prolonged painful episode, resulting in the release of inflammatory mediators, which led to multi-organ involvement and the development of adverse outcomes. Another possible explanation is that patients with prolonged painful episodes are treated more aggressively and that treatment leads to adverse outcomes. To explore this further, we modeled prolonged painful episode it as a dependent variable. We found that those with severe pain are more likely to develop prolonged painful episodes (OR=2.1, 1.1-4.9). History of CVA was also a predictor for prolonged painful episodes (OR=9.9, 1.8-53.3). This wide confidence interval indicates that a history of CVA is rare. We did not find any studies that looked at prolonged painful episodes as a predictor of adverse outcomes.

Young patients less than 8 years old were more likely to develop clinically significant outcomes (OR=2.4; 1.001-5.9). Mean age at death of 5.6 years was reported.[5] Almost 50% of sickle cell disease patients died before their 5th decade of life.[14] A prospective study reported that the peak incidence of death among children with sickle cell anemia occurred between 1 and 3 years of age, with most patients dying due to sepsis.[36] This indicates that younger patients are likely to develop more severe outcomes. Younger patients have immature immune systems and are less likely to mount a full response to infection, which could explain their risk of developing adverse outcomes.

Patients with lower oxygen saturation and experiencing chest crackles were more likely to develop clinically significant outcomes. This result was expected as they either predict or part of the clinical presentation of acute chest syndrome. Patients who appear toxic were more likely to have adverse outcomes (OR=7.8; 2.2-27.2). This indirectly indicates that emergency physicians could predict patients who appear toxic and ultimately will develop adverse outcomes. This supports the term we always use - that the patient looks toxic or is not looking well - to help emergency physicians make a decision about the disposition of the patient. There were no previous studies that looked at this specific variable as a predictor of adverse outcomes.

Splenomegaly increased the risk of developing adverse outcomes (OR=2.6; 1.2-5.5) and serves as an indicator of sequestration crisis, which is one of the clinically significant outcomes. To explore this theory, we did a univariate analysis which showed that patients with splenomegaly were more likely to have splenic sequestration crisis than those who did not (p-value=0.003). However, splenic sequestration was too uncommon in our study to allow for subgroup analysis.

Local limb tenderness lowered the chance of developing clinically significant outcomes (OR=0.23; 0.08-0.66). Our study is the first study to show that this is an important clinical variable. It is possible that patients with local limb tenderness are unlikely to have a severe episode and the sickling happens only in isolated part of the body. Another explanation is that local tenderness indicates that the vassocclusion happens in a superficial part of the body, like the periosteal area and not in the deep organs. It is proposed that centrally mediated reflexes, triggered by skin cooling, causes the shunting of the blood away from the bone marrow, which may account for the symmetrical and bilateral distribution of the pain.[58] This might lead to sickling in the bone and tenderness. The same pathophysiologic process is unlikely to cause other significant adverse outcomes.

The patients with severe anemia (defined as a hemoglobin level of less than 7 g/dl) were 3.6 times as likely to have severe disease as patients with hemoglobin levels of at least 7 g/dl (95%CI 1.1-11.6). Similarly, high reticulocytes (more than 15%) count increased the chance of developing adverse outcomes (OR=4.0; 1.4-11.5). Both are likely to predict the same clinical finding. We chose to keep both variables in the model as increases in the reticulocyte count lags a few days behind the acute decrease in the hemoglobin. The reticulocyte count is also an important variable to diagnosis aplastic crisis where the bone marrow fails to synthesize enough red blood cells to compensate for the insult, which causes a drop in hemoglobin. A low hemoglobin level has previously been shown to correlate with an increased risk of death in childhood[14] or adulthood, as well as an increased risk of stroke.[19] Perhaps low hemoglobin indicates a severe disease.

Other studies have found that low steady haemoglobin is important in predicting stroke and cardiomyopathy.[58]

Our study is unique in that it is predicting adverse outcomes in the acute setting and we are trying to predict the adverse outcomes using emergency department visit and variables. This is more clinically important in the management of the acute episodes. Long term outcome is more important for the chronic management of these patients and for the overall comprehensive management. The p-value for regular hydroxyurea was 0.46 and therefore was not entered in the multivariate model. To avoid removing it from the model just because of its high p-value, we explored the analysis by including it in the multivariate analysis and this again did not show that it was an important variable to include.

The area under the ROC curve was 0.88, indicating that our model has excellent ability to discriminate between those subjects who experienced adverse outcomes versus those who did not.[59] The Hosmer-Lemeshow goodness of fit statistic, did not indicate lack of fit. Figure 3 indicates that our model has a high sensitivity at low cut-off values and has a high specificity at higher cut-off values and that the specificity does not change significantly at a cut-off point of 0.4 or more. We are comfortable that our model is a fairly good model in predicting what it is intended to predict and that it is statistically plausible.

5.7 Multivariate Analysis to Determine the Clinical Predictors for Acute Chest Syndrome (Objective 5):-

The definition of acute chest syndrome requires the appearance of a new infiltrate on the chest x-ray, accompanied by acute respiratory symptoms.[60] It is the second most common reason for hospital admission for patients with sickle cell disease.[61] Our study confirmed these findings. It was the most common clinically significant adverse outcome. The following variables were found to be statistically significant and therefore were kept in the final logistic regression model: prolonged painful episode, oxygen saturation less than 92%, history of cough, chest crackles, and reticulocytes more than 15%. Two variables were found to decrease the chance of developing adverse outcomes: the presence of local limb tenderness and pneumococcal vaccination. All the variables were thought to be clinically relevant and therefore kept in the model. Prolonged painful episodes, local limb tenderness, and high reticulocytes counts were discussed in the previous section and would apply to acute chest syndrome as it is part of the clinically significant outcomes. Prolonged painful episodes, in particular, could be associated with acute chest syndrome. Prolonged painful episode means a more severe vaso-occlusive crisis. This might lead to a pulmonary fat embolism, which has been implicated in the pathophysiology of acute chest syndrome. It is believed that a pulmonary fat embolism most likely results from bone marrow necrosis, with the release of fat droplets in the blood stream which travels to the lung, initiating the fat embolism syndrome.[62-64]

Low oxygen saturation, cough, and chest crackles obviously favor the diagnosis of acute chest syndrome. They are part of the clinical findings in diagnosing acute chest syndrome. We decided to keep these variables in the model to emphasize the clinical

findings as an important part of acute chest syndrome diagnosis, in addition to the chest infiltrates on the chest x-ray. Also, we kept it in the model because most of the cases of acute chest syndrome (79%) developed after the hospital admission, while these findings were collected during the emergency department visits. Low oxygen saturation had a wide confidence interval around the point estimate (OR=17.68; 95% CI 1.67 - 184.93), because there were only few cases of low oxygen saturation in the acute chest syndrome group (3cases). A previous study indicated that pulse oximetry is often inaccurate in children with SCD, particularly in the face of severe anemia.[65] Although we did not study the accuracy of the oxygen saturation in our cohort, we do not believe that this conclusion will hold true in our study. Choosing a cut-off value of saturation of less than 96% would narrow the confidence interval, but might not be very meaningful clinically, hence we choose the cut-off point as 92%. Cough is a nonspecific respiratory symptom which could be caused by many etiologies. Chest crackles are likely caused by fluid in the alveoli or other inflammatory process in the lungs. It is important to recognize that chest x-ray findings could be subtle in the initial phase and a high index of suspicion is important. Morris et al. has shown that new pulmonary infiltrates often are missed by evaluating physicians.[66] This makes the clinical symptoms crucial, as acute chest syndrome could be rapidly fatal.

Patients who received a pneumococcal vaccination had an OR=0.33 (95% CI 0.11-0.98), indicating that pneumococcal vaccination might protect against the development of acute chest syndrome. This was not a surprising result, as infection has been implicated as a causative factor in the development of acute chest syndrome. However, pneumococcal infection had been isolated in a small number of patients who

developed acute chest syndrome.[47] One possibility is that pneuomococcal infection is more common than we previously thought, or that our population is different and pneumococcal infection is common in our cohort. These results should be replicated in future studies before reaching a firm conclusion about the pneumococcal vaccine. We do not have enough information about the use of Pneumococcal Conjugate Vaccine (Prevnar) in sickle cell disease patients and whether it might be protective against acute chest syndrome. Regular use of penicillin had a trend to be protective, but did not reach a statistical significance. It could be one variable to be tested in future studies.

The area under the ROC curve is 0.89. This indicates that our model has an excellent ability to discriminate between those subjects who developed acute chest syndrome versus those who did not. The Hosmer-Lemeshow goodness of fit statistic does not indicate lack of fit. Figure 4 indicates that our model has a high sensitivity at low cut-off values and has a high specificity at higher cut-off values and that the specificity does not change significantly at a cut-off point of 0.3 or more. We are comfortable that our model is a fairly good model for predicting what it is intended to predict and it is statistically plausible.

5.8 Baseline Vital Signs and Laboratory Parameters in Sickle Cell Disease Patients (Objectives 6 and 7):-

Table 9 shows the baseline vital signs and laboratory parameters. The mean heart rate for patients less than 8 years old was significantly higher than those who are older than 8 years (112 versus 94). The mean respiratory rate and systolic blood pressure was also significantly higher in younger patients. These results were expected. The mean diastolic blood pressure was not statistically significant between the two groups. The

mean temperature and oxygen saturation was similar between the two groups. These results were also expected. Furthermore, these results are similar to the general population; hence the baseline vital signs for sickle cell disease patients should be the same as for other patients.[67]

The mean white blood cell count is 13.9. The mean was the same across the different age cut-off values. The mean hemoglobin was significantly different in children less than 8 years old, compared to children older than 8 (8.6 versus 9.6). A possible explanation for this difference is that children younger than 8 years old are having rapid turnover of red blood cells and having increased synthesis of new blood cells. This is supported by the fact that younger patients have higher reticulocyte counts compared to older children and adults (10.7% versus 7.2%).

The laboratory parameters were measured during an acute visit to the emergency department. Although we are comfortable that these values represent the actual baseline values for the patients, we recommend using baseline laboratory parameters measurements during a routine visit and not during the acute episode to avoid bias. Patients who present in acute episodes are probably more likely to have abnormal laboratory parameters. The mean electrolytes in patients with sickle cell disease are not different from the mean electrolytes in the general population, hence we recommend using the general population standard parameters.[68] It was thought that dehydration might precipitate sickling and painful crisis. Patients with sickle cell disease are more prone to dehydration to decreased ability of the kidney to concentrate urine, which leads to increased urine output and dehydration.[69] The laboratory parameters do not show

evidence of dehydration as a potential precipitating factor. The BUN, creatinine, and serum bicarbonate level were within the normal limits.

5.9 Missing Data:-

Almost all studies have some missing observations.[70] We looked at sources of missing data and we reviewed the data collection sheets and charts to fill in any missing data. The main source for our missing observations was the laboratory parameters. The study protocol did not require investigations for all patients, so only 51% of the patients have laboratory investigations performed. The physicians did not believe that all of their patients required laboratory investigations. The physicians were likely more experienced in managing sickle cell disease patients and did not believe that laboratory investigations were required in all the patients. Listwise deletion (removing variables with missing observation) creates an unacceptable loss of data. It will also bias our results, leading to smaller parameters point estimates and a larger variance, because the more sick patients are more likely to have laboratory investigations. We discussed the best method for dealing with the missing data. We chose to do multiple imputation, which has been shown to produce less biased results in comparison to other methods. Janssen used multiple simulations to investigate issues of missing data and concluded that multiple imputations resulted in less biased regression coefficients, a better discriminative value, a better coverage, and a higher power than dropping the variable from the analysis. He continued to conclude that multiple imputations should be the method of first choice when dealing with missing values in (medical) research, even when the percentage of missing values is over 50%.[71] Another study proved that multiple imputation allows the

conservation of precious data observations and leads to unbiased estimates in consequent analyses.[78] We used multiple imputation techniques in SAS to impute the missing observations. The method we used was the Markov Chain Monte Carlo (MCMC) method with a single chain.[72] Instead of filling in a single value for each missing value, multiple imputation replaces each missing value with a set of plausible values that represent the uncertainty about the right value to impute.[73] We used all of the variables which will be used in the analysis to impute the missing observations. The dependent variables were not used in the imputation. We generated five data sets, and then we analyzed the five complete data sets using the logistic regression methods. Finally, the results from the five complete data sets were combined to produce inferential results. We believe this will produce less biased results than listwise deletion. We performed a sensitivity analysis for our model with and without the laboratory variables which were imputed. All the variables for clinically significant outcome were found to be predictors for adverse outcome. History of splenectomy was an extra variable to be included in the model without imputation. The following variables were included; removing the laboratory variables which had the maximum missing observations: a prolonged painful episode (OR 7.5; 95%CI 3.7-15.1), age less than 8 years (OR 5.7; 95%CI 2.3 -14.1), oxygen saturation less than 96% (OR 3.2; 95%CI 1.2-8.6), patient appearing toxic (OR 5.3; 95%CI 1.1-25.1), presence of chest crackles (OR 11.9; 95%CI 3.1-46.0), splenomegaly (OR 3.2; 95%CI 1.4-7.2), local limb tenderness (OR 0.2; 95%CI 0.06-0.6), history of splenectomy (OR 0.08; 95%CI 0.01-0.7). History of splenectomy should be tested further in future studies.

Strengths of the Study:-

We collected the data prospectively, which provides us with a blinded assessment of the outcome. The data was collected prior to the outcome, which provides reasonable evidence of association between the independent variables and the outcome. We performed univariate analysis and advanced multivariate analysis.

This study was the only one conducted in the emergency department, looking at potential adverse outcomes in the short term. We developed a detailed protocol before commencing the study. Patients from different age groups were enrolled. To minimize selection bias, we enrolled patients prospectively and consecutively, 24 hours a day during the study period. Then, we followed the patients prospectively and achieved a very high follow-up rate (95%). We searched our hospital database to explore the patients who lost follow-up, and we did not find any evidence that they developed adverse outcomes. By collecting the data on over 732 patients, we were able to enrol 75 patients with adverse outcomes and estimate the odds of developing adverse outcomes with a 95% confidence interval. We were able to estimate the univariate association between independent variables and the outcomes. We were also able to develop a logistic regression model to estimate the potential predictors for adverse outcomes. We demonstrated that our model had an excellent discriminatory power as shown in the ROC curves.

5.11 Limitations of the Study:-

Several potential limitations exist in our study. With the exception of acute chest syndrome, a small number of individual adverse outcomes within the clinically significant adverse outcomes made it impossible to evaluate the predictors for each

specific adverse outcome. Despite the fact that patients were identified prospectively, some variables were collected retrospectively and in some cases documentation was incomplete. The variables for admitted patients were collected from the chart as per study protocol. We did not include variables like the percentage of fetal hemoglobin and sickle hemoglobin as variables. There is a potential for misclassification bias. For example, acute chest syndrome might be misclassified as pneumonia and vice versa, which might bias our results in either way. However, we don't believe this will impact our results as pneumonia and acute chest syndrome are almost identical in patients with sickle cell disease. A potential for recall bias in some collected variables exists. Current medications and past medical history variables are potential sources for the recall bias. Patients who had a significant event in the past are more likely to remember it than those who did not. This would bias the results away from the null hypothesis. However; we tried minimizing this by reviewing the charts to collect most of the information in the past medical history. We did not require all patients to have the same investigations and treatment. It is likely that sicker patients are more likely to be investigated with laboratory tests. Almost half of the patients did not have laboratory investigations. This might also bias our results away from the null hypothesis. We explored this hypothesis by asking whether patients who had laboratory investigations done are more likely to have a clinically significant outcome or acute chest syndrome. There was no evidence from our results to support this hypothesis and the statistical test was not significant (p-value >0.1). We included patients from various age groups, but we do not believe that this will bias our results, as age is modeled as a variable in the study as a categorical variable. We did not subject our variables to interobserver variability as it was logistically difficult due to departmental

staffing. This limitation has to be addressed in the future. There was a lack of uniformity of ordering tests for these patients. In the protocol, we did not have a care map for these patients. It was difficult to start a new care map for the purpose of the study only. Our model has been not been validated, and therefore it should be validated prospectively.

5.12 Generalizability:-

Our study was conducted in one tertiary care center and this limits the generalizability of the results. Also, our study enrolled patients from one ethnic background, which might limit generalizability of the results to other ethnic backgrounds. Our model seems to have an excellent discriminatory power. We believe that the best use of this prognostic model is to classify patients as having more severe disease. Our model makes clinical sense, because the sicker the patients, the more likely they will develop adverse outcomes. It has a potential to be used in deciding which patients are likely to need aggressive therapy and hospital admission and which patients can be safely discharged home.

5.13 Future Research:-

There were 75 cases of clinically significant outcomes. We expect to enrol 150 cases in one year, if the enrolment is extended for another six months in the study site. The Royal hospital (another tertiary hospital in the region) has 55,000 patient visits per year and provides a tertiary care emergency service. It could be another site for the future study. As such, we expect to have 300 positive outcomes per year if we would conduct the study. Similarly, we would have approximately 160 positive outcomes for acute chest syndrome. This would provide us an excellent opportunity to derive clinical decision rules for acute chest syndrome and clinically significant outcomes.

Future research is needed to derive a clinical decision rule that can predict the adverse outcomes in patients with sickle cell disease. The study should incorporate the information gained from this study. An attractive study would be to establish a daycare hospital to manage painful vaso-occlusive crisis. From our study, we found the admission rate to be as high as 32.6%. An interventional study by establishing a day care, in attempt to reduce hospital admission will be feasible

Clinical prediction rules are decision-making tools for clinicians, containing variables from the history, physical examination, or simple diagnostic tests.[74] Methods for clinical decision rules have been described and, in particular: the outcomes and predictive variables must be clearly defined; blind assessment of outcomes and predictive variables should be done; and the rules should prospectively validated. Reproducibility of predictive variables should be assessed and the rules should make clinical sense.[75] Based on the results of our study, the rate of clinically significant adverse outcomes was 10.2%. To derive the rule, we will include 30 variables which were found to be clinically and statistically important. We would likely discard 50% of these variables after the univariate analysis. Hence, we would require 1500 patients. We would be able to achieve this target within one year, if we would expand our recruitment to include two tertiary care hospitals. For acute chest syndrome, we would need two years to achieve our target. The validation phase will likely require the same number to achieve acceptable sensitivity and specificity. In addition, a longer follow-up will be needed to avoid missing potential adverse outcomes.

An intervention study evaluating the establishment of a daycare hospital to manage sickle cell disease patients is interesting. This will likely improve the patients

care and reduce admission. Sickle cell disease is a lifelong syndrome; reducing admission will greatly impact the patient's quality of life. We would randomize patients to either a day care hospital group or emergency department group. Our null hypothesis is that day care does not reduce hospital admission nor does save money. To be effective program, we will assume that the daycare hospital will reduce the admission rate from 32% to 16%. The sample size required in each group will be 123 patients to achieve a power of 0.80 with level of significance of 0.05. Provided we have the same recruitment rate, we would likely be able to conduct the study over a 2- month period.

5.14 Conclusions:-

In this study, we have demonstrated that 10% of patients with sickle cell disease develop clinically a significant adverse outcome and 5.7% develop acute chest syndrome. We have demonstrated that there were no previous studies conducted in the emergency department to address the predictors of adverse outcomes in sickle cell disease patients. We were able to derive a model to predict clinically significant adverse outcomes and acute chest syndrome in the emergency department.

We found several variables that were highly related to clinically significant outcomes. The patients who developed clinically significant outcomes were more likely to be younger, present with fever, had a prolonged painful episode, received blood transfusions, had chest pain, and had a history of splenic sequestration crisis. Furthermore, these patients were more likely to have tachycardia, oxygen saturation less than 96%, appear toxic, had a respiratory rate >24, a temperature >38.0, a pain numeric

score >8.0 and had chest crackles. They were also more likely to have wbc >12, hb <7g/dl, had reticulocytes >15%.

We found several variables that were highly related to developing acute chest syndrome. The patients who developed acute chest syndrome are more likely to be male, present with fever, had a prolonged painful episode, complained of shortness of breath, cough, and had chest pain, a history of blood transfusion and a history of splenectomy. Patients were more likely to be febrile, have tachycardia, have oxygen saturation less than 92%, to appear toxic, display a pain visual analogue score >8.0, and had chest crackles. They were more likely to have wbc >12 and higher reticulocyte count. They were less likely to appear well.

The final logistic regression model for clinically significant outcome was: age less than 8 years old, prolonged painful episode, oxygen saturation less than 96%, patients appearing toxic, chest crackles, splenomegaly, hemoglobin less than 7 g/dl, and reticulocytes more than 15%. The presence of local limb tenderness was one variable that was found to decrease the chance of developing adverse outcomes. The logistic regression model for acute chest syndrome includes prolonged painful episode, oxygen saturation less than 92%, history of cough, chest crackles, and reticulocytes more than 15%. Two variables decrease the chance of developing adverse outcomes: presence of local limb tenderness and pneumococcal vaccination.

Future research should look more closely into developing clinical prediction rules with high sensitivity to predict the adverse outcomes. Our model makes clinical sense, because the sicker the patients, the more likely they will develop adverse outcomes.

Table 1: Important Clinical Manifestations of Sickle Cell Disease

Acute Manifestations
Painful vaso-occlusive crisis*
Bacterial sepsis * **
Osteomyelitis* Due to salmonella and *Staphylococcus aureus***
Splenic sequestration*
Aplastic crisis**
Acute chest syndrome*
Cerebrovascular Accidents*
Priapism*
Hematuria and papillary necrosis*
Chronic manifestations
Anemia**
Jaundice**
Splenomegaly*
Functional asplenia*
Cardiomegaly **
Cholelithiasis**
Delayed growth and sexual maturation**
Restrictive lung disease*
Pulmonary hypertension*
Avascular necrosis
Proliferative retinopathy
Leg ulcers*
Transfusional hemosiderosis

*	manifestations due to vaso-occlusion
**	manifestations due to hemolysis
***	infectious manifestations

Table 2: List of History Variables Collected by Physician or Research Assistant for Sickle Cell Disease Study for the Emergency Visit

	Variables Collected	
Demographics	• Age (years) • Gender (male/female	• Date of emergency visit (d/m/y) • Physician status (resident/physician)
Presenting Complaints	• Does the patient had pain(Yes/No) its severity, location and duration • Does the patient had fever (Yes/No) • History of shortness of breath, cough or runny nose(Yes/No)	• History of headache(Yes/No) • History of vomiting, or diarrhoea (Yes/No)
Past Medical History	• Age of SCD diagnosis(years) • History of splenic sequestration and splenectomy(Yes/No) • History of ICU admission (Yes/No) • History of cholecystectomy (Yes/No) • Vaccinations history (Pneumococcal, meningococcal and H. Influenza) (Yes/No)	• History of CVA(Yes/No) • History of blood transfusion (regular or exchange transfusions (Yes/No) • Regular medications(NSAIDS, antibiotics, folic acid and hydroxyurea) (Yes/No)

Table 3: List of Physical Examination, Investigation and Treatment Variables Collected by Physician or Research Assistant for Sickle Cell Disease Study for the Emergency Visit

	Variables Collected	
Physical Examination	• Temperature (degrees Celsius) • Heart rate (beats per minute) • Blood pressure(Systolic blood pressure (mm of Hg) and Diastolic blood pressure (mm of Hg)) • Oxygen saturation (%) • Appearance of the patient(does the patient appears lethargic or toxic) • Pain scale(numeric score) • Does the patient appeared jaundice(Yes/No) • Does the patient appeared pale(Yes/No) • Does the patient chest have crackles(Yes/No)	• Does the patient have focal neurological deficits(Yes/No) • Does the patient have neck stiffness(Yes/No) • Abnormal throat Examination(Yes/No) • Does the patient have abdominal tenderness(Yes/No) • Does the patient have hepatomegaly or splenomegaly(Yes/No) • Does the patient have localized tenderness(Yes/No
Investigations	• CBC if yes(Hb, WBC, Platelets counts) • Reticulocytes if yes (%) • INR(ratio of normal) • LFT if yes(Bilirubin, AST, ALT)	• Chest x-ray if yes(normal or abnormal) • Electrolytes if yes(Na, K, Cl HCO3) • Urea, Creatinine if yes
Treatment in the ED and Disposition	• Intravenous fluids(Yes/No) • Intravenous narcotics(Yes/No) • Intravenous Antibiotics(Yes/No)	• Patient Admitted(Yes/No) • Probability of the patient to have a repeat emergency visit

Table 4: List of Variables Collected for the Admitted and Telephone Follow-up Patients

	Variables Collected	
Variables for the Admitted Patients	• Use of intravenous narcotics if yes(duration) • Use of intravenous or oral antibiotics if yes(duration) • ICU admission if yes(duration) • Blood cultures if yes(positive or negative)	• Chest x-ray if yes(normal or abnormal) • Outcome (dead or alive) • Discharge diagnosis
Variables Collected During Telephone Follow-up	• Number of attempts to reach the patient • Is the patient alive if not(when did he die) • Did the patient need to visit the emergency in the last 2 weeks(Yes/No) if yes(When, where and why)	• Did the patient have worsening of the condition for which he visited the emergency(Yes/No) if yes(what did you do) • Did the patient have recurrence of the same episode for which he visited the emergency(Yes/No) • Did the patient develop a different problem since the last visit(Yes/No)

Table 5: History Characteristics of the 732 Patients with Sickle Cell Disease

Characteristics	N=732	%
Demographics		
Mean Age (SD)	20.4	8.4
Range	1-48	
Females %	287	39.2%
Presenting Problems	N	%
Pain	674	92.0%
Fever	79	10.8%
Dizziness	30	4.1%
Shortness of Breath	39	5.3%
Cough	53	7.2%
Runny nose	46	6.3%
Chest Pain	82	11.2%
Headache	39	5.3%
Vomiting	34	4.6%
Diarrhea	14	1.9%
Lethargy	50	6.8%
Past Medical History	N	%
History of CVA	21	2.9%
History of Transfusion	128	17.5%
History of Splenectomy	94	12.8%
History of Splenic Sequestration	125	17.1%
Frequent Painful Episode(>2/month)	359	49.0%
History of Cholecystectomy	90	12.3%
History of ICU admission	136	18.6%
Vaccination		
H.influenza Vaccine	77	10.5%
Pneumococcal Vaccine	175	23.9%
Meningococcal Vaccine	79	10.8%
Regular Medications	N	%
Penicillin	563	76.8%
Hydroxyurea	222	30.3%
Codeine	452	61.7%
NSAIDS	610	83.2%
Folic Acid	621	84.7%
Other Narcotics	106	14.5%

Table 6: Physical Examination and Laboratory Features of the 732 Patients with Sickle Cell Disease

Characteristics	N=732	
Vital Signs	Mean	SD
Temperature	36.9	0.78
Range	30.0-40.8	
Heart Rate	95.9	18.32
Range	40-180	
Respiratory Rate	21.2	3.19
Range	10-38	
SBP(mmhg)	113.3	15.14
Range	67-178	
DBP(mmhg)	64.4	11.73
Range	40-110	
O2 Saturation (%)	98.9	2.21
Range	79.0-100	
Physical Examination	N=732	%
Appears Well	300	40.9%
Appears Lethargic	152	20.7%
Appears Toxic	17	2.3%
Splenomegaly	79	10.8%
Hepatomegaly	48	6.5%
Abdominal Tenderness	55	7.5%
Local Redness	34	4.6%
Local Warm	60	8.2%
Local Tenderness	159	21.7%
Local Swelling	45	6.1%
General Pallor	249	34.0%
Chest crackles	21	2.9%
Throat Redness/Exudate	38	5.2%
Abnormal Cardiac Exam	3	0.4%
Pain Score(SD)	2.1	5.7
Treatment in the ED	N=732	%
Intravenous Fluids	583	79.5%
Intravenous Antibiotics	28	3.8%
Laboratory Features	Mean	SD
White blood cells	12.2	6.5
Range	2.7-69.9	
Hemoglobin(g/dl)	9.5	1.6

Range	4.4-13.9	
Platelets	369.9	202.3
Range	50.0-1706.0	
Reticulocyte (%)	7.6	5.1
Range	0.8-30.8	
Na(mmol/l)	137.4	2.7
K(mmol/l)	4.1	0.4
Hco3(meq/l)	23.7	3.3
Urea(mmol/l)	2.9	1.2
Creat(μmol/l)	37.6	17.6
ALT(U/l)	76.0	40.6
AST(U/l)	58.5	53.6
Total Bilirubin(mmol/l)	81.0	72.2

Table 7: Baseline Characteristics for the Excluded Patients for the Sickle Cell Disease Study

Characteristics	N=314	%
Demographics		
Mean Age (SD) yrs	22.0	8.2
Range	2-48	
Females (%)	132	42.0%
Presenting Problems	**N**	**%**
Pain	275	87.6%
Fever	22	7.0%
Shortness of Breath	10	3.2%
Cough	53	7.2%
Past Medical History	**N**	**%**
History of CVA	4	1.3%
Vaccination		
H. Influenza Vaccine	51	16.2%
Pneumococcal Vaccine	86	26.1%
Meningococcal Vaccine	46	14.6%
Regular Medications	**N**	**%**
Penicillin	217	69.1%
Hydroxyurea	79	25.2%
Vital Signs	**Mean**	**SD**
Temperature	36.9	0.78
Heart Rate	92.2	14.97
Respiratory Rate	21.5	4.6
SBP(mmhg)	113.2	14.60
O2 Saturation (%)	99.02	2.01
Physical Examination	**N**	**%**
General Pallor	76	24.2%
Chest crackles	3	1.0%
Pain Score(SD)	2.00	5.7
Treatment in the ED		**%**
Intravenous Fluids	221	70.4%
Intravenous Antibiotics	12	3.8%
Laboratory Features	**Mean**	**SD**
White blood cells	11.24	5.5
Hemoglobin(g/dl)	10.2	6.80
Platelets	350.1	174.3
Reticulocyte (%)	8.3	9.07

Table 8: Outcome Ascertained for the Sickle Cell Disease Patients

Outcome	Number of Patients (N=732)	%
Admitted to the Hospital	308	42.1%
Clinically Significant Outcome	75	10.2%
Death	2	0.3%
Acute Chest Syndrome	42	5.7%
Splenic Sequestration Crisis	13	1.8%
Sepsis	8	1.1%
Hyperhemolyitc crisis	6	0.8%
CVA	1	0.1%
Exchange Blood Transfusion	3	0.4%

Table 9: Characteristics of the Patients with Sickle Cell Disease who were Admitted Patients and Patients Requiring Telephone Follow-up within 2 Weeks of ED Presentation

Characteristics	Number of Patients(N=308)	
Patients Admitted	**308**	**%**
Demographics		
Mean Age (SD)	19.34	8.5
Range	(1-48)	
Female (%)	124	40.3%
Severe Painful Episodes	244	79.2%
Treatment Received		
Antibiotics	50	16.2%
Narcotics	261	84.7%
Admission to ICU	8	2.6%
Abnormal Chest X-ray	68	22.1%
Patients Discharged Alive	307	99.7%
Patients who had Telephone Follow-up(2 weeks)	**N=152**	
Demographics		
Mean Age (SD)	17.9	8.8
Range	(1-48)	
Female	54	36.0%
Died Within 2 weeks	1	0.6%
Repeat ED visits	12	7.9%
Recurrence of the Same Episode	14	9.2%
New Clinical Problem	11	7.2%

Table 10: The Baseline Mean Vital Signs and Laboratory Features for the Sickle Cell Disease Patients Stratified by Age

Variables	Mean	SD
Temperature(Celsius)*		
Age <=8	36.9	0.8
Age >8	36.9	0.8
O2 Saturation (%)*		
Age <=8	99.5	1.3
Age >8	98.9	2.2
Heart rate**		
Age <=8	112.0	19.0
Age >8	94.0	17.0
Respiratory Rate**		
Age <=8	25.0	4.0
Age >8	20.0	2.0
SBP(mmhg)**		
Age <=8	104.0	14.0
Age >8	114.0	15.0
Hb(g/dl)**		
Age <=8	8.6	1.9
Age >8	9.6	1.6
Reticulocyte count (%)**		
Age <=8	10.7	7.9
Age >8	7.2	4.6
WBC*		
Age <=8	12.8	5.7
Age >8	11.9	6.8
Na(mmol/l)*		
Age <=8	136.0	2.0
Age >8	137.0	3.0
K(mmol/l)*		
Age <=8	4.0	0.3
Age >8	4.1	0.4
HCO3(meq/l)*		
Age <=8	23.7	2.8
Age >8	24.2	3.5
Urea(mmol/l)*		
Age <=8	2.7	0.9
Age >8	2.9	1.3
Creatinine(µmol/l)*		
Age <=8	28.0	12.0
Age >8	40.0	19.0

*No statistical difference among age groups

** P-value < 0.05 for variables stratified by age of 8 years.

Table 11: Univariate Correlation of Variables from History for Clinically Significant Outcomes for the Sickle Cell Disease Study

	Negative Outcome		Positive Outcome		
	N=657	%	N=75	%	P-Value
Demographics					
Age (SD)	20.7	(8.1)	18.1	(10.1)	0.02*
Age Less than 8 years	38	5.8%	13	17.3%	<0.001*
Females	265	40.3%	22	29.3%	0.07*
Presenting Problems					
Prolonged Painful Episodes(>72 hrs)	111	16.9%	38	50.7%	<0.001*
Pain	610	92.8%	64	85.3%	0.02*
Dizziness	26	4.0%	4	5.3%	0.56
Fever	64	9.7%	15	20.0%	0.007*
Shortness of Breath	32	4.9%	7	9.3%	0.10
Cough	38	5.8%	15	20.0%	<0.001*
Runny nose	38	5.8%	8	10.7%	0.09
Chest Pain	65	9.9%	17	22.7%	0.001*
Headache	37	5.6%	2	2.7%	0.27
Vomiting	24	3.7%	10	13.3%	<0.001*
Diarrhea	13	2.0%	1	1.3%	0.69
Lethargy	41	6.2%	9	12.0%	0.06
Past Medical History					
History of CVA	20	3.0%	1	1.3%	0.40
History of Transfusion	104	15.8%	24	32.0%	<0.001*
History of Splenectomy	91	13.9%	3	4.0%	0.01*
History of Splenic Sequestration	106	16.1%	19	25.3%	0.04*
Frequent Painful Episode(>2/month)	325	49.5%	34	45.3%	0.49
History of Cholecystectomy	82	12.5%	8	10.7%	0.65
History of ICU admission	121	18.4%	15	20.0%	0.73
Vaccination					
H. Influenza Vaccine	69	10.5%	8	10.7%	0.96
Pneumococcal Vaccine	154	23.4%	21	28.0%	0.38
Meningococcal Vaccine	75	11.4%	4	5.3%	0.10
Regular Medications					
Penicillin	505	76.9%	58	77.3%	0.92
Hydroxyurea	202	30.7%	20	26.7%	0.46
Codeine	418	63.6%	34	45.3%	0.002*

NSAIDS	547	83.3%	63	84.0%	0.87
Folic Acid	557	84.8%	64	85.3%	0.89
Other Narcotics	99	15.1%	7	9.3%	0.18

* p-value < 0.05 is Statistically Significant for the Univariate Association

Table 12: Univariate Correlation of Variables from Physical Examination for Clinically Significant Outcomes for the Sickle Cell Disease Study

Clinically Significant Outcome					
	Negative Outcome		Positive Outcome		
	N=657	%	N=75	%	P-Value
Vital Signs					
Temperature (SD)	36.9	(0.8)	36.9	(0.8)	0.45
Heart Rate (SD)	95.0	(17.1)	104.2	(24.8)	<0.001*
Respiratory Rate (SD)	21.1	(3.1)	22.1	(3.7)	0.01*
Systolic blood pressure (SD)	113.6	(14.8)	110.8	(17.4)	0.13
Oxygen saturation (SD)	99.0	(2.0)	98.0	(3.2)	<0.001*
Temperature >38	34	5.2%	8	10.7%	0.05*
Heart Rate >110	112	17.0%	29	38.7%	<0.001*
Respiratory Rate >24	48	7.3%	12	16.0%	0.01*
Systolic blood pressure >100	119	18.1%	20	26.7%	0.08
Oxygen saturation <96%	41	6.2%	14	18.7%	<0.001*
Physical Examination					
Pain Severity (SD)	6.6	(1.9)	6.9	(2.4)	0.55
Pain Score(SD)	5.6	(2.0)	6.6	(2.6)	0.02
Pain Severity >6(patient Rating)	176	26.8%	14	18.7%	0 .22
Pain Score >8	23	3.5%	6	8.0%	0.001*
Appears Well	277	42.2%	23	30.7%	0.050*
Appears Lethargic	138	21.0%	14	18.7%	0.60
Appears Toxic	10	1.5%	7	9.3%	<0.001*
Splenomegaly	62	9.4%	17	22.7%	<0.001*
Hepatomegaly	40	6.1%	8	10.7%	0.12
Abdominal Tenderness	46	7.0%	9	12.0%	0.12
Local Redness	33	5.0%	1	1.3%	0.24
Local Warm	58	8.8%	2	2.7%	0.07
Local Tenderness	154	23.4%	5	6.7%	0.001*
Local Swelling	41	6.2%	4	5.3%	0.75
General Pallor	203	30.9%	46	61.3%	<0.001*
Chest crackles	10	1.5%	11	14.7%	<0.001*
Throat Redness/Exudate	35	5.3%	3	4.0%	0.6 2

*p-value <0.05 is Statistically Significant for the Univariate Association

Table 13: Univariate Correlation of Variables from Emergency Department Treatment and Laboratory Features for Clinically Significant Outcomes for the Sickle Cell Disease Study

Clinically Significant Outcome					
	Negative Outcome		Positive Outcome		
Treatment Received in ED	N=657	%	N=75	%	P-Value
Intravenous Fluids	529	80.5%	54	72.0%	0.08
Intravenous Antibiotics	23	3.5%	5	6.7%	0.17
Laboratory investigations					
White Blood Cells (SD)	12.0	(6.5)	13.9	(6.6)	0.08
Hemoglobin (SD)	9.7	(1.5)	8.4	(1.9)	<0.001*
Platelets (SD)	375	(204)	327	(185)	0.14
Reticulocyte (SD)	6.9	(4.1)	12.2	(8.0)	<0.001*
Urea (SD)	2.9	(0.9)	3.0	(1.7)	0.68
Ast (SD)	52.7	(63.1)	56.5	(42.6)	0.81
Total Bilirubin (SD)	71.5	(90.2)	74.0	(46.70	0.91
White Blood Cells >12 (n=374)	125	19.0%	25	33.3%	0.03*
Hemoglobin <7g/dl (n=374)	8	1.2%	14	18.7%	<0.001*
Platelets <180 (n=374)	242	36.8%	29	38.7%	0.05*
Reticulocyte >10% (n=374)	49	7.5%	22	29.3%	<0.001*
Reticulocyte >15% (n=374)	15	2.3%	14	18.7%	<0.001*
Urea >2 (n=374)	52	7.9%	15	20.0%	0.08
Ast >100 (n=374)	2	0.3%	1	1.3%	0.73
Total Bilirubin >30 (n=374)	35	5.3%	15	20.0%	0.42

*p-value <0.05 is Statistically Significant for the Univariate Association

Table 14: Final Model Developed by Stepwise Logistic Regression Analysis to Predict Clinically Significant Outcomes from Sickle Cell Disease Study

Variable	Coefficient	Odds Ratio (95% CI)	P-Value
Prolonged Painful episode	2.3	10.1 (5.2-19.3)	<0.001*
Patient Appear Toxic	2.0	7.8 (2.2-27.2)	0.001*
Chest Crackles	1.8	6.5 (2.2 -18.6)	<0.001*
Reticulocytes > 15%	1.3	4.0 (1.4-11.4)	0.01*
Oxygen Saturation < 96 %	1.3	3.9 (1.6-10. 9)	0.003*
Hemoglobin < 7g/dl	1.2	3.6 (1.1 - 11.5)	0.03*
Splenomegaly	0.9	2.6 (1.1 -5.5)	0.02*
Age < 8 years	0.8	2.4 (1.001-5.9)	0.05*
Local Limb Tenderness	-1.4	0.2 (0.08-0.6)	0.006*

* p-value< 0.05 is Statistically Significant

Table 15: Univariate Correlation of Variables from History for Acute Chest Syndrome for the Sickle Cell Disease Study

Acute Chest Syndrome					
	Negative Outcome		Positive Outcome		
	N=690	%	N=42	%	P-Value
Demographics					
Mean Age (SD)	20.3	(8.3)	21.4	(9.5)	0.48
Age Less than 8 years	50	7.2%	1	2.4%	0.40
Females	277	40.1%	10	23.8%	0.03*
Presenting Problems					
Prolonged Painful Episodes (>72 hrs)	120	17.4%	29	69.0%	<0.001*
Pain	633	91.7%	41	97.6%	0.17
Dizziness	29	4.2%	1	2.4%	0.56
Fever	67	9.7%	12	28.6%	0.03*
Shortness of Breath	33	4.8%	6	14.3%	0.008*
Cough	41	5.9%	12	28.6%	<0.001*
Runny nose	43	6.2%	3	7.1%	0.81
Chest Pain	67	9.7%	15	35.7%	<0.001*
Headache	38	5.5%	1	2.4%	0.38
Vomiting	29	4.2%	5	11.9%	0.02*
Diarrhea	14	2.0%	0	.0%	0.35
Lethargy	47	6.8%	3	7.1%	0.93
Past Medical History					
History of CVA	21	3.0%	0	.0%	0.93
History of Transfusion	116	16.8%	12	28.6%	0.05*
History of Splenectomy	93	13.5%	1	2.4%	0.04*
History of Splenic Sequestration	121	17.5%	4	9.5%	0.2
Frequent Painful Episode (>2/month)	339	49.1%	20	47.6%	0.84
History of Cholecystectomy	84	12.2%	6	14.3%	0.96
History of ICU admission	127	18.4%	9	21.4%	0.62
Vaccination					
H. Influenza Vaccine	74	10.7%	3	7.1%	0.46
Pneumococcal Vaccine	169	24.5%	6	14.3%	0.13
Meningococcal Vaccine	78	11.3%	1	2.4%	0.07
Regular Medications					

Penicillin	534	77.4%	29	69.0%	0.21
Hydroxyurea	208	30.1%	14	33.3%	0.66
Codeine	430	62.3%	22	52.4%	0.20
NSAIDS	574	83.2%	36	85.7%	0.67
Folic Acid	585	84.8%	36	85.7%	0.87
Other Narcotics	101	14.6%	5	11.9%	0.62

* p-value < 0.05 is Statistically Significant for the Univariate Association

Table 16: Univariate Correlation of Variables from Physical Examination for Acute Chest Syndrome for the Sickle Cell Disease Study

Acute Chest Syndrome					
	Negative Outcome		Positive Outcome		
	N=690	%	N=42	%	P-Value
Vital Signs					
Temperature (SD)	36.8	(0.7)	37.1	(1.0)	0.09
Heart Rate (SD)	95.7	(17.9)	100.0	(23.9)	0.13
Respiratory Rate (SD)	21.2	(3.1)	21.7	(3.7)	0.32
Systolic blood pressure (SD)	113.2	(14.9)	115.8	(18.2)	0.27
Oxygen saturation (SD)	99.0	(1.9)	97.0	(4.0)	<0.001*
Temperature >38.0	36	5.2%	6	14.3%	0.01*
Heart Rate>110	128	18.6%	13	31.0%	0.05
Respiratory Rate>24	54	7.8%	6	14.3%	0.13
Systolic blood pressure >100	133	19.3%	6	14.3%	0.41
Oxygen saturation<92%	3	0.4%	3	7.1%	0.003*
Physical Examination					
Pain Severity-Patient Rating (SD)	6.5	(2.0)	7.6	(1.3)	0.06
Pain Score(SD)	5.6	(2.0)	7.3	(2.0)	0.003*
Pain Severity >6(patient Rating)	179	25.9%	11	26.2%	0.09
Pain Score>8	24	3.5%	5	11.9%	<0.001*
Appears Well	291	42.2%	9	21.4%	0.008*
Appears Lethargic	143	20.7%	9	21.4%	0.93
Appears Toxic	14	2.0%	3	7.1%	0.03*
Splenomegaly	74	10.7%	5	11.9%	0.81
Hepatomegaly	46	6.7%	2	4.8%	0.63
Abdominal Tenderness	50	7.2%	5	11.9%	0.27
Local Redness	34	4.9%	0	.0%	0.14
Local Warm	59	8.6%	1	2.4%	0.16
Local Tenderness	156	22.6%	3	7.1%	0.02
Local Swelling	43	6.2%	2	4.8%	0.70
General Pallor	227	32.9%	22	52.4%	0.01*
Chest crackles	11	1.6%	10	23.8%	<0.001*
Throat Redness/Exudate	37	5.4%	1	2.4%	0.40

*p-value <0.05 is Statistically Significant for the Univariate Association

Table 17: Univariate Correlation of Variables from Emergency Department Treatment and Laboratory Features for Acute Chest Syndrome for the Sickle Cell Disease Study

	Acute Chest Syndrome				
	Negative Outcome		Positive Outcome		
	N=690	%	N=42	%	P-Value
Treatment Received in ED					
Intravenous Fluids	552	80.0%	31	73.8%	0.33
Intravenous Antibiotics	25	3.6%	3	7.1%	0.25
Laboratory investigations					
White Blood Cells (SD)	11.9	(6.3)	16.6	(7.5)	0.001*
Hemoglobin (SD)	9.5	(1.6)	9.2	(1.6)	0.50
Platelets (SD)	369.6	(204.0)	372.9	(180.3)	0.94
Reticulocyte (SD)	7.5	(5.0)	9.1	(6.2)	0.15
Urea (SD)	2.9	(1.2)	2.7	(0.9)	0.44
Ast (SD)	52.7	(59.1)	59.3	(57.1)	0.75
Total Bilirubin (SD)	72.9	(85.7)	67.6	(45.6)	0.85
White Blood Cells >12	132	19.1%	18	42.9%	0.001*
Hemoglobin<7g/dl	19	2.8%	3	7.1%	0.19
Platelets<180	182	26.4%	15	35.7%	0.50
Reticulocyte>10%	62	9.0%	9	21.4%	0.03*
Reticulocyte>15%	24	3.5%	5	11.9%	0.02*
Urea>2	58	8.4%	9	21.4%	0.09
Ast>100	2	0.3%	1	2.4%	0.35
Total Bilirubin>30	43	6.2%	3	7.1%	0.85

*p-value <0.05 is Statistically Significant for the Univariate Association

Table 18: Final Model Developed by Stepwise Logistic Regression Analysis to Predict Acute Chest Syndrome from Sickle Cell Disease Study

Variable	Coefficient	Odds Ratio (95% CI)	P-Value
Prolonged Painful Episode	3.1	22.0 (8.7 -55.3)	<0.001*
Oxygen Saturation < 92%	2.9	17.7 (1.7 - 184.9)	0.02*
Chest Crackles	2.3	9.5 (2.6-34.7)	< 0.001*
Reticulocyte count >15%	1.6	4.9 (1.2-19.7)	0.03*
History of Cough	1.5	4.5 (1.7 -12.0)	0.003*
History of Pneumococcal Vaccine	-1.1	0.33 (0.11-0.98)	0.047*
Local Limb Tenderness	-1.6	0.2 (0.05-0.8)	0.02*

*p-value < 0.05 is Statistically Significant

Table 19: Univariate Correlation for Patients with Fever

	Temp<38.0		Temp>=38.0		
	N=688	%	N=44	%	P-value
Hospital Admission	274	40.0%	27	61.4%	0.02*
Revisited ED Within 2 Weeks	228	33.1%	10	22.7%	0.20
Clinically Significant Outcome	65	9.4%	8	18.2%	0.049*
Prolonged Painful Episode	141	20.5%	6	13.6%	0.31
Acute Chest Syndrome	35	5.1%	6	13.6%	0.01*

*p-value <0.05 is Statistically Significant for the Univariate Association

Table 20: Summary of Sensitivity and Specificity for Classification Table based on the Logistic Regression model for the Acute Chest Syndrome Using a Cut Point of 0.003 to 0.95

Classification Cut Off	Sensitivity	Specificity
0.95	0.0%	100.0%
0.9	7.1%	99.8%
0.8	7.1%	99.7%
0.7	11.9%	99.7%
0.6	14.2%	99.7%
0.5	19.0%	99.5%
0.4	28.5%	99.2%
0.3	28.5%	98.4%
0.2	71.4%	92.3%
0.1	83.8%	87.9%
0.05	88.1%	81.1%
0.04	88.1%	78.1%
0.03	88.1%	76.6%
0.02	88.1%	72.9%
0.01	95.2%	34.9%
0.003	100.0%	14.0%

Table 21: Summary of Sensitivity and Specificity for Classification Table Based on the Logistic Regression Model for the Clinically Significant Outcome Using a Cut point of 0.01to 0.95

Classification Cut Off	Sensitivity	Specificity
0.95	1.4%	100.0%
0.9	1.4%	100.0%
0.8	4.2%	100.0%
0.7	8.4%	99.6%
0.6	21.1%	99.2%
0.5	28.1%	97.9%
0.4	43.6%	96.8%
0.3	56.4%	93.3%
0.2	64.7%	90.1%
0.1	83.1%	79.4%
0.05	85.9%	69.9%
0.04	92.9%	60.6%
0.03	95.7%	55.2%
0.02	95.7%	46.0%
0.01	98.5%	19.2%

Figure 1: Genetic Variables in Sickle Cell Disease

Genetic Variants	Hb(g/liter)	% Hb A	% Hb F	% Hb A_2a	Reticulocytes(%)	Severity	% of patients
Hb SS	78	0	4.6	2.8	10.1	4	65
Hb SC	90	0	4.0	2.0		2	25
Hb S-β^0-thal	89	0	5.9	5.0	7.2	4	2
Hb S-β^+-thal	84-115	5–30	6.0	4.8	1.5-8%	1-3	8
Hb S-HPFH	146	0	25.8	1.9	2.4	0	<1

1. Hb: Hemoglobin
2. HbA: Normal Hb
3. HbF: fetal Hb that remains expressed at 2 years of age and older
4. HPFH: Sickle cell-hereditary persistence of fetal hemoglobin
5. Severity according to genotype: a qualitative ranking from 0-4. There is great variability within each genotype

Figure 2: Study Flow of 6-Months Prospective Cohort Study of Emergency Patients with Sickle Cell Disease

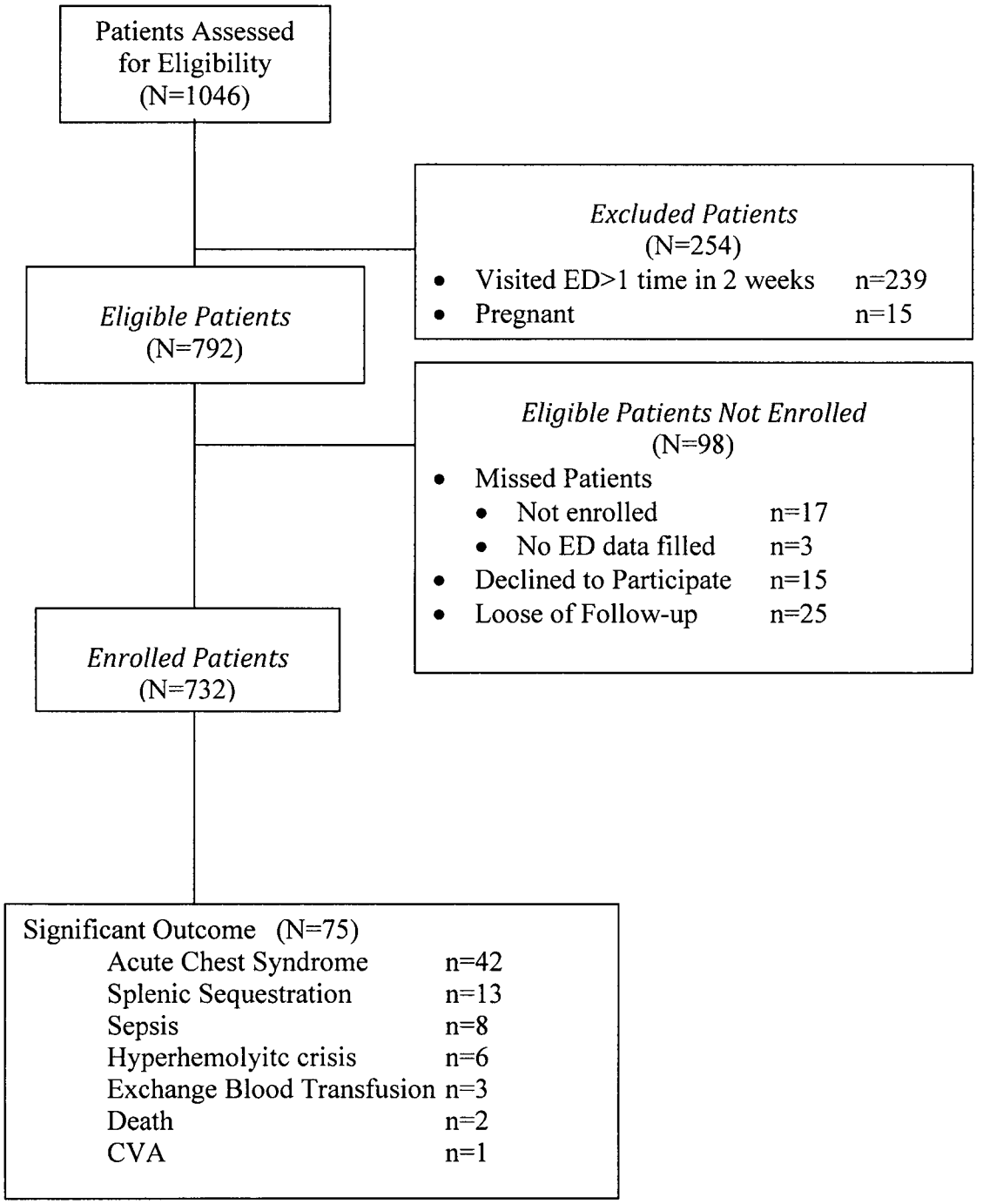


Figure 3: Plot of Sensitivity and Specificity versus All Possible Cutpoints of the Final Logistic Regression Model for Clinically Significant Outcome in the Sickle Cell Disease Study

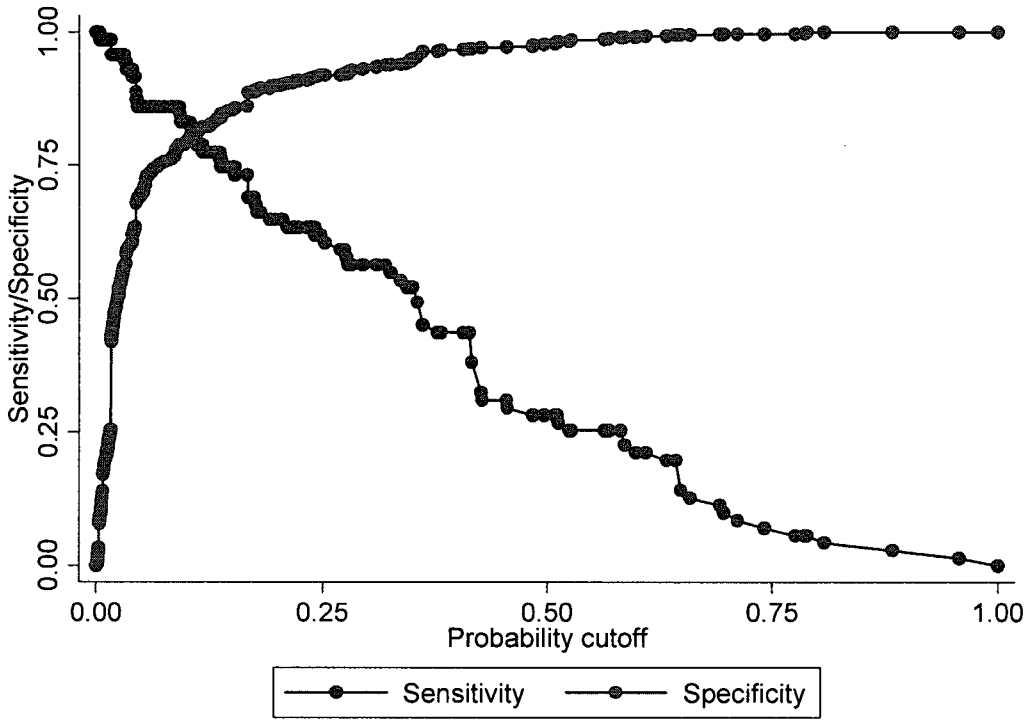


Figure 4: Receiver Operating Characteristic (ROC) Curve of the Final Model for Clinically Significant Outcomes for the Sickle Cell Disease Study

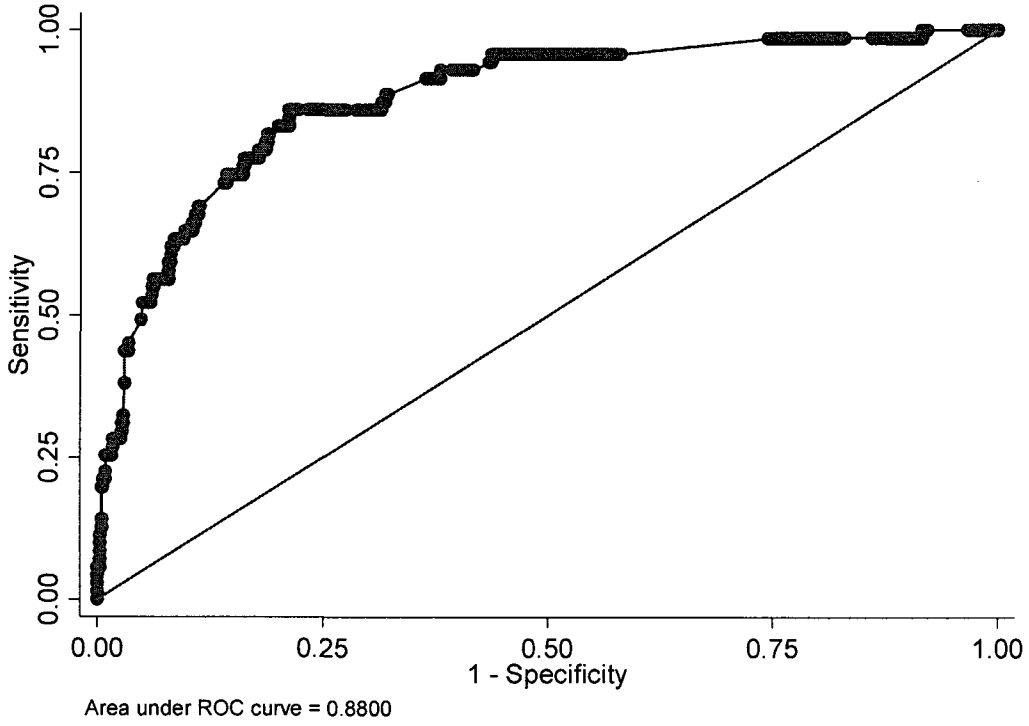


Figure 5: Plot of Sensitivity and Specificity versus All Possible Cutpoints of the Final Logistic Regression Model for Clinically Significant Outcome in the Sickle Cell Disease Study

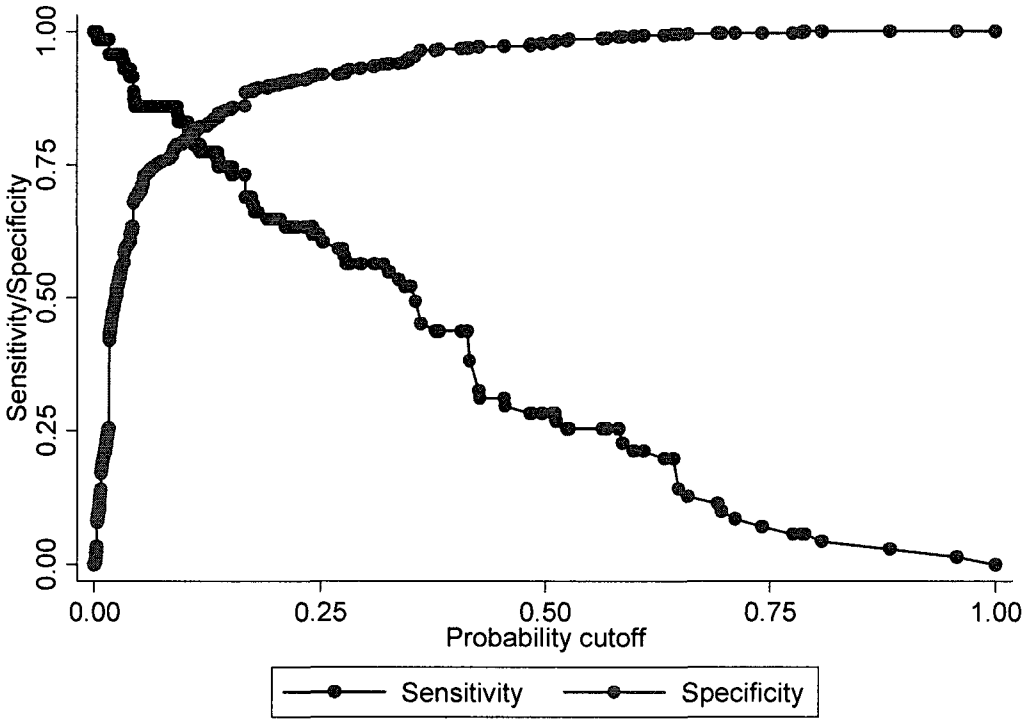
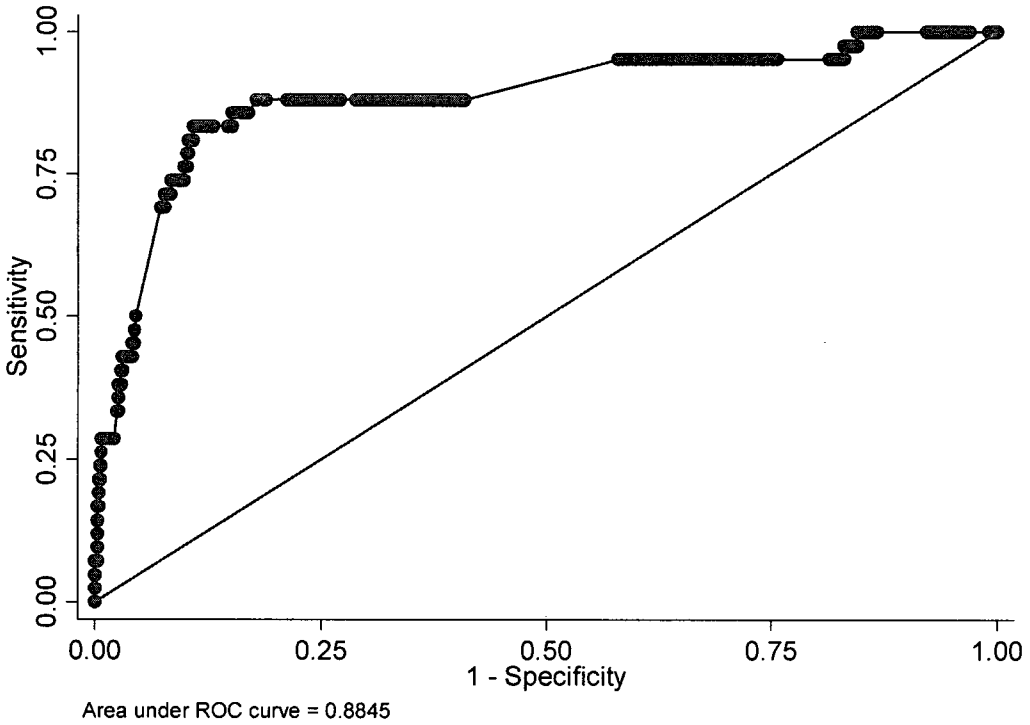


Figure 6: Receiver Operating Characteristic (ROC) Curve of the Final Model for Acute Chest Syndrome Outcomes for the Sickle Cell Disease Study



BIBLIOGRAPHY

1. Taber's Cyclopedic Medical Dictionary, 20th Edition.

2. Segal JB, Strouse JJ, Beach MC, Haywood C, Witkop C, Park H, Wilson RF, Bass EB, Lanzkron S. Hydroxyurea for the treatment of sickle cell disease. Evid Rep Technol Assess (Full Rep). 2008 Mar;(165):1-95.

3. Bunn HF. Pathogenesis and treatment of sickle cell disease. N Engl J Med 1997 Sep 11;337(11):762-9.

4. Kaul DK. Fabry ME. Costantini F, Rubin EM, Nagel RL. In vivo demonstration of red cell-endothelial interaction, sickling and altered microvascular response to oxygen in the sickle transgenic mouse. J Clin Invest 1995 Dec;96(6):2845-53.

5. Quinn CT, Rogers ZR, Buchanan GR. Survival of children with sickle cell disease. Blood 2004;103(11):4023– 7.

6. Savitt TL, Goldberg MF (1989). "Herrick's 1910 case report of sickle cell anaemia. The rest of the story". JAMA 261 (2): 266-271

7. Desai DV, Dhanani H. Sickle Cell Disease: History and Origin. The Internet Journal of Hematology. 2004. Volume 1 Number 2: 1540-2649

8. Hoffman: Hematology: Basic Principles and Practice, 4th ed.

9. Wethers DL. Sickle Cell Disease in Childhood. Am Fam Physician 2000; 62:1013-20,1027-8.

10. Bainbridge R. Higgs DR. Maude GH, Serjeant GR. J Pediatr 1985 Jun;106(6):881-5

11. Brozovic M, Anionmu J. Sickle cell disease in Britain. J Clin Pathol 1984 Dec; 37(12):1321-6.

12. Platt OS, Thorington BD, Brambilla DJ, Milner PF, Rosse WF, Vichinsky E, Kinney TR. Pain in sickle cell disease. Rates and risk factors, N Engl J Med. 1991 Jul 4;325(1):11-6.

13. Overturf GD. Infections and immunizations of children with sickle cell disease. Adv Pediatr Infect Dis 1999;14:191-218.

14. Leikin SL, Gallagher D, Kinney TR, et al. Mortality in children and adolescents with sickle cell disease. Cooperative Study of Sickle Cell Disease. Pediatrics 1989;84:500-8.

15. Gill FM, Sleeper LA, Weiner SJ, et al. Clinical events in the first decade in a cohort of infants with sickle cell disease. Cooperative study of sickle cell disease. Blood 1995;86:776-83.

16. Shankar SM. Talbot TR, Arbogast PG, Mitchel EF, Wang WC, Schaffner W, Craig AS, Griffin MR. Incidence of invasive pneumococcal disease among individuals with sickle cell disease before and after the introduction of the pneumococcal conjugate vaccine. Halasa Clin Infect Dis. 2007 Jun 1;44(11):1428-33. Epub 2007 Apr 18.

17. Powars D, Overturf G, Turner E. Is there an increased risk of Haemophilus influenzae septicemia in children with sickle cell anemia? Pediatrics 1983 Jun;71(6):927-31.

18. Dean D, Neumayr L, Kelly DM, Ballas SK, Kleman K, Robertson S, Iyer RV, Ware RE, Koshy M, Rackoff WR, Pegelow CH, Waldron P, Benjamin L, Vichinsky E. Chlamydia pneumoniae and acute chest syndrome in patients with sickle cell disease. J Pediatr Hematol Oncol 2003 Jan;25(1):46-55.

19. Ohene-Frempong K, Weiner SJ, Sleeper LA, Miller ST, Embury S, Moohr JW, Wethers DL, Pegelow CH, Gill FM. Cerebrovascular accidents in sickle cell disease: rates and risk factors. Blood 1998 Jan 1;91(1):288-94.

20. Emond AM, Collis R, Darvill D, Higgs DR, Maude GH, Serjeant GR. Acute splenic sequestration in homozygous sickle cell disease: natural history and management. Pediatr 1985 Aug;107(2):201-6.

21. Rao SP, Miller ST, Cohen BJ. Transient aplastic crisis in patients with sickle cell disease. B19 parvovirus studies during a 7-year period. Am J Dis Child 1992 Nov;146(11):1328-30.

22. Serjeant GR, Serjeant BE, Thomas PW, et al. Human parvovirus infection in homozygous sickle cell disease. Lancet 1993;341:1237– 40.

23. Petz LD, Calhoun L, Shulman IA, Johnson C, Herron RM. The sickle cell hemolytic transfusion reaction syndrome, Transfusion 1997 Apr;37(4):382-92.

24. Vichinsky EP, Styles LA, Colangelo LH, Wright EC, Castro O, Nickerson B. Acute chest syndrome in sickle cell disease: clinical presentation and course. Cooperative Study of Sickle Cell Disease; Blood 1997 Mar 1;89(5):1787-92.

25. Martin CR, Johnson CS, Cobb C, Tatter D, Haywood LJ. Myocardial infarction in sickle cell disease J Natl Med Assoc 1996 Jul;88(7):428-32.

26. Rees DC, Olujohungbe AD, Parker NE, Stephens AD, Telfer P, Wright J. Guidelines for the management of the acute painful crisis in sickle cell disease. Br J Haematol 2003 Mar;120(5):744-52.

27. Wilimas JA, Flynn PM, Harris S, Day SW, Smith R, Chesney PJ, Rodman JH, Eguiguren JM, Fairclough DL, Wang WC. Randomized study of outpatient treatment with ceftriaxone for selected febrile children with sickle cell disease, Engl J Med 1993 Aug 12;329(7):472-6.

28. Falletta JM, Woods GM, Verter JI, Buchanan GR, Pegelow CH, Iyer RV, Miller ST, Holbrook CT, Kinney TR, Vichinsky E. et al. Discontinuing penicillin prophylaxis in children with sickle cell anemia. Prophylactic Penicillin Study II Pediatr 1995 Nov;127(5):685-90.

29. Sox CM. Cooper WO. Koepsell TD. DiGiuseppe DL. Christakis DA.. JAMA Provision of pneumococcal prophylaxis for publicly insured children with sickle cell disease 2003 Aug 27;290(8):1057-61.

30. Wong WY. Overturf GD,Powars DR. Clin Infect Dis 1992 May;14(5):1124-36. Infection caused by Streptococcus pneumoniae in children with sickle cell disease: epidemiology, immunologic mechanisms, prophylaxis, and vaccination.

31. Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on the frequency of painful crisis in sickle cell anemia. N Engl J Med 1995;332:1317–1322.

32. Davies S, Olujohungbe A. Hydroxyurea for sickle cell disease. In: The Cochrane Library, Issue 3, 2006. Chichester, UK: John Wiley & Sons, Ltd.

33. Ferster A, Vermylen C, Cornu G, et al. Hydroxyurea for treatment of severe sickle cell anemia: a pediatric clinical trial. Blood 1996;88:1960–1964.

34. Steinberg MH, Barton F, Castro O, Pegelow CH, Ballas SK, Kutlar A, Orringe E, et al. Effect of Hydroxyurea on Mortality and Morbidity in Adult Sickle Cell Anemia: Risks and Benefits Up to 9 Years of Treatment, JAMA. 2003;289:1645-1651

35. Brozovic M, Davies SC, Brownell AI. Acute admissions of patients with sickle cell disease who live in Britain. Br Med J (Clin Res Ed) 1987; 294:1206.

36. Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in sickle cell disease: life expectancy and risk factors for early death. N Engl J Med. 1994;330:1639-1644.

37. Motulsky AG. Frequency of sickling disorders in U.S. blacks. N Engl J Med 1973;288:31– 3.

38. Overturf GD, Powars D, Baraff LJ. Bacterial meningitis and septicemia in sickle cell disease. Am J Dis Child 1977 Jul;131(7):784-7

39. Houston-Yu P, Rana SR, Beyer B, Castro O. Frequent and prolonged hospitalizations: a risk factor for early mortality in sickle cell disease patients. Am J Hematol 2003 Mar;72(3):201-3.

40. Al-Riyami AA, Suleiman AJ, Afifi M, Al-Lamki ZM, Daar S. A community-based study of common hereditary blood disorders in Oman. East Mediterr Health J. 2001; 7(6):1004-11.

41. Miller ST, Sleeper LA, Pegelow CH, et al. Prediction of adverse outcomes in children with sickle cell disease. N Engl J Med 2000; 342:83.

42. Goldberg M, Brugnara C, Dover G,Schapira L, Charache S and Bunn H. (1990). Treatment of sickle cell anemia with hydroxyurea and erythropoietin. N Eng J Med 323, 366-372.

43. Manci EA, Culberson DE, Yang YM, et al. Causes of death in sickle cell disease: an autopsy study. Br J Haematol 2003; 123:359.

44. Adams RJ, McKie VC, Hsu L, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med 1998; 339:5.

45. Rogers ZR, Morrison RA, Vedro DA, Buchanan GR. Outpatient management of febrile illness in infants and young children with sickle cell anemia. J Pediatr 1990; 117:736.

46. Castro O, Brambilla DJ, Thorington B, et al. The Acute Chest Syndrome in Sickle Cell Disease- incidence and risk factors. Blood 1994; 84:643.

47. Vichinsky EP, Neumayr LD, Earles AN, Williams R. Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. N Engl J Med 2000; 342:1855.

48. Baum KF, Dunn DT, Maude GH, Serjeant GR. The painful crisis of homozygous sickle cell disease. A study of the risk factors. Arch Intern Med 1987; 147:1231.

49. Meremikwu MM. Sickle cell disease update. BMJ Clin Evid 2007;08:2402

50. Clark E, Plint AC, Correll R, Gaboury I, Passi B. A randomized, controlled trial of acetaminophen, ibuprofen, and codeine for acute pain relief in children with musculoskeletal trauma.Pediatrics. 2007 Mar;119(3):460-7. Erratum in: Pediatrics. 2007 Jun;119(6):1271.

51. Frei-Jones MJ, Baxter AL, Rogers ZR, Buchanan GR.Vaso-occlusive episodes in older children with sickle cell disease: emergency department management and pain assessment. J Pediatr. 2008 Feb;152(2):281-5. Epub 2007 Oct 24.

52. Raphael JL, Kamdar A, Wang T, Liu H, Mahoney DH, Mueller BU. Day hospital versus inpatient management of uncomplicated vaso-occlusive crises in children with sickle cell disease.Pediatr Blood Cancer. 2008 Feb 25.

53. Raphael JL, Kamdar A, Beavers MB, Mahoney DH, Mueller BU. Treatment of uncomplicated vaso-occlusive crises in children with sickle cell disease in a day hospital. Pediatr Blood Cancer. 2008 Jul;51(1):82-5.

54. Davies S, Olujohungbe A. Hydroxyurea for sickle cell disease. In: The Cochrane Library, Issue 3, 2006. Chichester, UK: John Wiley & Sons, Ltd.

55. Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on the frequency of painful crisis in sickle cell anemia. N Engl J Med 1995;332:1317–1322.

56. Al-Dabbous IA.Acute chest syndrome in sickle cell disease in Saudi Arab Children in the Eastern Province.Ann Saudi Med. 2002 May-Jul;22(3-4):167-71.

57. Serjeant GR, Chalmers RM. Current concepts in haemotology. Is the painful crisis of sickle cell disease a "steal" syndrome. J Clin Pathol 1990; 43:789-91.

58. Kinney TR, Sleeper LA, Wang WC, et al. Silent cerebral infarcts in sickle cell anemia: A risk factor analysis. The Cooperative Study of Sickle Cell Disease. Pediatrics 1999;103:640-5.

59. David W. Hosmer, Stanley Lemeshow, Applied logistic regression (Wiley Series in probability and statistics) 2nd edition,160-164

60. Castro O, Brambilla DJ, Thorington B, et al. The acute chest syndrome in sickle cell disease: Incidence and risk factors. The Cooperative Study of Sickle Cell Disease. Blood 1994;84:643-9.

61. Siddiqui AK, Ahmed S. Pulmonary manifestations of sickle cell disease. Postgrad Med J, 2003. 79(933): p. 384-90.

62. Johnson K, Stastny JF, Rucknagel DL. Fat embolism syndrome associated with asthma and sickle cell=b+-thalassemia. Am J Hematol 1994;46:354–7.

63. Vichinsky EP, Williams R, Das M, et al. Pulmonary fat embolism: a distinct cause of severe acute chest syndrome in sickle cell anemia. Blood 1994;83:3107–12.

64. Walters MC, Nienhuis AW, Vichinsky E. Novel therapeutic approaches in sickle cell disease. Hematology (Am Soc Hematol Educ Program), 2002: p. 10-34.

65. Blaisdell CJ, Goodman S, Clark K, et al. Pulse oximetry is a poor predictor of hypoxemia in stable children with sickle cell disease. Arch Pediatr Adolesc Med 2000;154:900– 3.

66. Morris C, Vichinsky E, Styles L. Clinician assessment for acute chest syndrome in febrile patients with sickle cell disease: is it accurate enough? Ann Emerg Med 1999;34:64–9.

67. Normal Vital Signs Reference for EMS, (website) emsresource.net/vitals.shtml

68. McPherson & Pincus: Henry's Clinical Diagnosis and Management by Laboratory Methods, 21st ed.

69. Saborio P, Scheinman JI. Sickle cell nephropathy. J Am Soc Nephrol 1999;10:187–192.

70. Altman DG, Bland JM. BMJ 2007;334(7590):424 (24 February)

71. Janssen KJM, Donders ART. Imputation of missing covariate values is always better than dropping the covariate, even with missing data percentages of up to 90% the 28th Annual Meeting of the Society for Medical Decision Making (October 15-18, 2006)

72. Schafer JL. (1997), Analysis of Incomplete Multivariate Data, New York: Chapman and Hall.

73. Rubin DB. (1976), "Inference and Missing Data," Biometrika, 63, 581–592.

74. Laupacis A, Sekar N, Stiell IG. Clinical Prediction Rules: A review and suggested modifications of methodological standards. JAMA 1997; 277(6):488-494.

75. Stiell IG, Wells GA. Methodologic standards for the development of clinical decision rules in emergency medicine. Ann Emerg Med 1999; 33(4):437-447.

76. Lanzkron S, Strouse JJ, Wilson R, Beach MC, Haywood C, Park H, Witkop C, Bass EB, Segal JB. An Evidence-based Review for the NIH Consensus Development Conference on Hydroxyurea for the Treatment of Adults with Sickle Cell Disease. Ann Intern Med. 2008 May 5.

77. DORIS L. WETHERS. Sickle Cell Disease in Childhood. Am Fam Physician 2000; 62:1013-20,1027-8

78. Moore L, Lavoie A, LeSage N, Liberman M, Sampalis JS, Bergeron E, Abdous B.Multiple imputation of the Glasgow Coma Score. J Trauma. 2005 Sep;59(3):698-704.

Appendix A: Starting Dose for the Opiate Analgesia

Usual Starting Doses of Opioid Analgesics in Opioid-Naive Adults

Usual Starting Dose for Moderate to Severe Pain		
Medication	**Parenteral**	**Oral**
Morphine	0.3 mg/kg every 3-4 h	0.1-0.15 mg/kg every 2-4 h
Hydromorphone (Dilaudid)	0.06-0.08 mg/kg every 3-4 h	0.015-0.020 mg/kg every 3-4 h
Meperidine(Demerol)	not recommended (1.1-1.75 mg/kg every 3-4 h if necessary after evaluation).	not recommended (0.75-1.0 mg/kg, every 3-4 h if necessary after evaluation).)
Combination opioid/NSAID preparations		
Codeine with acetaminophen	0.5-1mg/kg every 3-4 h	not recommended
Oxycodone	0.15-0.20 mg/kg every 3-4 h	not available

Appendix B: Infections and Associated Microorganisms

Clinical Disease	Common Micro-organisms
Fever without source	*Streptococcus pneumonia* *Hemophilus influenzae*
Meningitis	*Streptococcus pneumonia* *Hemophilus influenzae*
Chest syndrome	*Streptococcus pneumonia* *Mycoplasma pneumoniae*
Osteomyelitis/septic arthritis	*Salmonella* *Staphylococcus aureus*
Urinary tract infection	*Streptococcus pneumoniae* *Escherichia coli* *gram-negative enterics*

Appendix C: Verbal Consent Structure

مستشفى جامعة السلطان قابوس-قسم الطواري

عنوان الدراسه: الحالات الطارئه للانيميا المنجليه- دراسه شامله

مكان الدراسه: قسم الطواري بجامعة السلطان قابوس

موضوع الدراسه:

من المعروف ان الانيميا المنجليه مرض مزمن يصاحبه العديد من الالم وقد يصاحبه بعض المضاعفات الخطيره. دراسة الحالات الطارئه للانيميا المنجليه و تشمل دراسة اسباب زيارة الطواري والاعراض المصاحبه لها والمضاعفات المصاحبه التي قد تنتج عن هذا المرض.

الهدف من هذه الدراسه:

هو دراسة المضاعفات التي قد تنتج عن الانيميا المنجليه اثناء وبعد زيارت قسم اطواري. معرفة هذه المضاعفات سيؤدي الى وضع استراتيجيه لتجنت او التقليل من احتمال حدوث هذه المضاعفات وتقديم خدمات افضل اثناء زيارتكم لقسم الطواري في المستقبل.

عند زيارتكم لقسم الطواري سيتم الفحص السريري والعلاج من قبل طبيب الطواري كما يتم في اي زياره طارئه وحسب درجة الاولويه والخطوره. سيقوم الطبيب بتقرير العلاج المطلوب ووصف اي علاج ضروري. سيقرر الطبيب اذا تطلب العلاج ادخالكم المستشفى لاكمال العلاج او اكمال العلاج في المنزل. سيتم مراجعة ملفكم الصحي بعد اخراجكم من المستشفى وتسجيل البيانات المطلوبه للدراسه.

في حالة خروجكم من قسم الطواري سيقوم الباحث بالمستشفى بالاتصال بكم وسؤالكم عدة اساله بالهاتف عن حالتكم الصحيه وعن احتمال وجود اي مضاعفات ناتجه عن مرضكم وكذلك عن زيارة اي مستشفى اخر. سيسغرق الاتصال اقل من خمسة دقائق

هذه الدراسه لاتحمل اي خطر او مضاعفات حيث انه لايوجد اي تجربه لاي دواء او علاج جديد. كل المعلومات ستضل خاصه بالمستشفى ولن يتم نشر اي معلومات شخصيه او خاصه.

تعاونكم لاكمال هذه الدراسه جد مهم ولكم مطلق الحريه في المشاركة او عدمه ولكم مطلق الحريه با الانسحاب من الدراسه في وقت ولن يؤثر ذلك في حال من الاحوال على جودة العلاج المقدم لكم الان او بالمستقبل.

مع تمنياتنا لكم بالشفاء العاجل

Appendix D: Data Collection for the Emergency Visit

Triage Section

Triage Nurse_____

Vital signs: Temp: ------ Heart Rate: --------Resp. Rate: ---------BP---------O2 Sat: -------

Chief Complaint (Reason for visit) 1. ---------- 2. ----------

Physician Section

History: Filled by_____

Type of SCD 1. SS 2. S/B-Thal. Major------ 3. S/B-Thal. Intermedia -------- Others----

What do you think the probability that this patient will be admitted today(please choose

1-5%--------- 6-20% -------21-40% ------41-60%--------61-80%----------81-100%----------

(I) Chief Complaint. Does the Patient have the following?

	Yes	No
Pain		
Dizziness		
Fever		
SOB		
Cough		
Runny Nose/Sneezing		
Headache		
Vomiting		
Diarrhea		
lethargy		
Others Specify_____		

II) Description of Symptoms :(please Choose one or more for each category)

1. **Pain: Severity as described by patient**

No Pain 0 1 2 3 4 5 6 7 8 9 10 *Worst Pain Possible*

Circle one number from 0 to 10

Duration **i) less than 1 day** **ii) 1-3 days** **iii) 3+days**

Localization of the Pain_____

2 Fever: Cause of Fever **i) URTI-----** **ii) Pneumonia----** **iii) UTI----**

iv) Meningitis---- **v) Others---------** **vi) not sure-----**

PMH:

1. Age of diagnosis of SCD----------

History Of The Following		Yes	No	No Information available
CVA/TIA				
Regular Blood transfusion				
Splenic Sequestration				
Splenectomy				
More than 2 painful episodes last month				
Cholecystectomy				
History of ICU admission				
H. influenza Immunization				
Pneumococcus Immunization				
Meningococcuss Immunization				
Family H/O SCD				
Regular Medications	Penicillin V			
	Hydroxyurea			
	Codeine			
	NSAIDS			
	Others Specify.....			

Physical Exam: -

Patient appearance: - Well looking-----, Lethargic-----, Toxic (very sick looking)----------

- In little pain----------, in severe pain----------
- How much do you rate the pain for this patient

No Pain 0 1 2 3 4 5 6 7 8 9 10 *Worst Pain Possible*

Circle one number from 0 to 10

General Exam: - Please do as appropriate and tick the relevant one if done

	Yes	No	Not sure

Looks Well			
Jaundice			
Pallor			
Chest-crackles			
Priapism			
Focal neurological deficit present			
Neck stifness			
Skin ulcer present			
	Normal	***Abnormal***	***Specify the abnormality***
Throat			
CVS			
Abdomen	**Tender** Yes No	Splenomegaly____ Hepatomegaly_____	**Spleen size=_____** **Liver size=_____**

Local Examination: Examination of the painful area (please Tick)

Redness_____ Warm_____Tender_____Swelling_____

Treatment in ED:

Did the patients receive the followings?

	Yes	**No**
IV fluids		
IV narcotics		
IV antibiotics		
Others Specify		

Outcome:

	Yes	**No**
Was the patient admitted		

What Is the Admitting/Discharge Diagnosis----------

Do you think the patient will revisit the emergency in next 2 weeks

YES(----) NO(---) Not sure(----)

What is the chance he will revisit ED in 2 weeks(please write a percentage from

(0-100%)------

Appendix E: Data Collection Form for the Admitted Patients

Patient Name_____

MRN_____

Date of Admission__/__/___

Duration of Admission---Days----------

Was there a need for 1. IV narcotics (Yes /No)

2. IV or new PO ANTIBIOTICS—SPECIFY----------

Duration of antibiotics----------

3. ICU admission (yes /No) ---why----------

Duration of Fever if febrile----------

Results of blood culture----------

Radiological investigation----------

Duration of Pain----------

Any surgical operation (Yes /N0) specify----------

Outcome: Discharged alive (yes/No) If dead what is the cause----------

Discharge Diagnosis----------

Appendix F: Structured Telephone Interview

Subject No.:_____ Requires Telephone on:(y/m/d)_____
Patient Name_____
MRN_____
Account Number_____

Sickle Cell Disease Emergency Study

TELEPHONE FOLLOW-UP (2 WEEKS)
FOR PATIENTS WHO DID NOT HAVE REPEAT EMERGENCY (WITHIN 2 WEEKS) VISITS OR ADMITTED

Hello, Can I speak to _____(Patient name or parent of patient)
Hi _____,
I am----------from the Emergency Department at the Sultan Qaboos University Hospital

I am calling about the sickle cell disease emergency visit follow-up study.
This research study is trying to determine the problems which patients like yourself might have after the discharge from the emergency so we can improve the quality of care you might receive in the future

We will take approximately 5 minutes to answer the following questions

Date and times of attempts:_____
Date Reached :(y/m/d)___/_____/_____
Dead?_____Date of Death(y/m/d)__/___/___Lost Follow Up?____ Refused?_____

1) a) Did you need to visit the emergency in the last 2 weeks? O Yes O No
If 'no' skip to question # 2
b) If 'yes' Answer the following:
When? Date(y/m/d)_____/_____/_____
How many times? _____
Did you get admitted? O Yes O No
When and where? Date(y/m/d)_____/____/_____ Where_____
How long did you take to recover? _____

What was the reason for the visit? Symtoms_____
2) a) Did you have any worsening of your condition for which you were seen in the emergency?
O Yes O No
If 'no' skip to question # 3
b) If 'yes' Answer the following

How long did you remain sick? _____
Did you see another health care professional since your last emergency visit?
O Yes O No
What did you do about it?_____
Describe the Problem?_____

3) a) Did you have recurrence of the same episode since your last visit?

O Yes **O No**

If 'no' skip to question # 4

b) If 'yes' Answer the following:

Did you recover or still having the symptoms?

O Yes **O No**

How long did you remain free of this symptom?_____

Please describe the episode?_____

4) a) Did you develop another(different from the first visit) symptom since your last visit?

O Yes **O No**

If 'no' Stop and thank you

b) If 'yes' Answer the following

Please describe the episode?_____

What did you do for that symptoms/episode?_____

Appendix G: Case Summary Form

Subject No.:_____

Sickle Cell Disease Study

CASE RECORD FORMS

(ELIGIBLE PATIENT WITH COMPLETED PHYSICIAN DATA FORM)

OUTSTANDING INFORMATION

(completed)	(to be completed)	
_____	_____	Initial Data collection sheet
_____	_____	Lab Investigations
_____	_____	Data admission form if admitted
_____	_____	Telephone Follow-up
_____	_____	Admission Information - Results of blood tests and investigations attched
_____	_____	Discharge Summary -attach discharge summary
_____	_____	Emergency Physician emergency Chart - attached copy

Any Adverse Outcome reported- as defined in the study

1. Repeat ED visit	**Yes**	**No**
2. Emergency Exchange blood transfusion	**Yes**	**No**
3. Splenic sequestration	**Yes**	**No**
4. Sepsis	**Yes**	**No**
5.CVA	**Yes**	**No**
6. Acute chest syndrome	**Yes**	**No**
7. Death	**Yes**	**No**
8. Hyperhemolytic crisis	**Yes**	**No**

Need admission	**Yes**	**No**
Prolonged painful VOC	**Yes**	**No**

DEMOGRAPHICS

Patient Initials: _____ **Chart no.:**_____

Visit Summary

Date of Visit:(yy/mm/dd) ____-____-___**Date of Birth:**(yy/mm/dd)_____

Sex: ± Male ± Female

Physician Status: Consultant-------- Resident(year)--------- Specialist----------
Interobserver? ± No ± Yes
If **'yes'**, physician code: _____

Transferred from another health care centre? ± No ± Yes

Sickle Cell Disease Study

HISTORY

Date of Visit:(yy/mm/dd) ____-____-_____
Onset Of Symtoms Number of days symptoms started_____

Presenting complains:

1. **2.**
3. **4.**

PMH: **1.** **2.**
3. **4.**

Physical examination: - Please list the positive findings only

1. **2.**
3. **4.**
5. **6.**

Treatment received in ED:

1. **Analgesia:** What drug, total doses in mg. how many doses and route

Medication: ----------Total dose----------Number of doses-----route------

2. **IV fluids:** Type, how much fluid in total----------

   ---
3. **Antibiotics:** What antibiotics ,dose, route----------

   ---
4. **Other medications:**----------

For discharged patients:

1. **What discharge medications(List) prescribed—**
   (dose,route,name)----------
   ---

2. **What regular medication the patient is taking-**1.----------
   ------2.----------3.----------
   ----4.----------
3. **Chance will develop sepsis**----------
   ---
4. **Chance will develop adverse outcome**----------

Admitted? No Yes
If 'yes', where? Ward Critical Care Unit Transfer
If 'yes', why? ---

For admitted patients :(attach the discharge summary) and result of blood test and X-ray

Repeat ED(SQUH) visit within 2 weeks of the initial visit- No need for follow up call

For repeat ED visit during 2 weeks of the index visit -please attach the ED copy visit

Please complete the same ED visit form

Data sheet completed? No Yes

Reason for repeat visit: ----------

Did the patient get admitted No Yes

If yes: - what was the reason----------

Please attach the discharge summary of the visit& complete the admission form-------

Discharge diagnosis----------

Attach the lab test results

If the patient visited ED more than 2 times over 2 weeks fill the same data form and same if got admitted or discharged

How many times the patient visited the ED in last 2 weeks (SQUH or another hospital)

For Discharged patients

Fill out the phone follow u form

Phones follow up date----------

Did the patient develop any adverse outcomes during 2 weeks No Yes

Did he need to be seen in another hospital----------when and reason-------

Please get the discharge summary for that visit if possible----------

Duration of illness ----------

Appendix H: Ethics Approval from the Sultan Qaboos University Hospital(Study Site)

Sultan Qaboos University
COLLEGE OF MEDICINE
& HEALTH SCIENCES

جامعة السلطان قابوس
كلية الطب
والعلوم الصحية

Our Ref SQ.U.C.M:RS/07/ 003

10th January 2007

To: Dr. Nabil Al Zadjali
Department Accident and Emergency

From: Prof. Mohammed Idris
Assistant Dean for postgraduate Studies & Research
Chairperson, Medical Research and Ethics Committee (MREC)

Subject: Research proposal: ***Sickle Cell Disease in the Emergency Department: A Prospective Cohort Study*** *(MREC 258)*

Thank you for submitting your above titled research proposal for review by MREC. The committee has reviewed your proposal on its meeting of 17th December and approved it.

On behalf of MREC I wish you a productive study.

Best wishes

P.O. Box : 35
Al-Khod, Sultanate of Oman
Postal Code 123
Telex: 5602 SQU ON Cable: Jami'ah
Telephone : (968) 24141103; Telefax (968) 24413419

صندوق البريد : ٣٥
الخوض – سلطنة عُمان
الرمز البريدي: ١٢٣
تلكس : ٥٦٠٢ إس كيو يو أو إن – برقيا: جامعة
هاتف: ٢٤١٤١١٠٣ (٩٦٨) ؛ فاكس: ٢٤٤١٣٤١٩ (٩٦٨)

Appendix I: Ethics Approval from the Ottawa Hospital Research Ethics Board

The Ottawa Hospital **L'HOpital d'Ottawa**

Research Ethics Board
Conseil d'ethique en recherches
798-5555 ext 14146,14902 or 15072
Fax No. - 761-4311
http://www.ohri.ca/ohreb/

Tuesday, April 08, 2008

Dr. Abdullah Al Reesi
Ottawa Hospital -
Civic Campus
Emergency
Department
1053 Carling Avenue
Ottawa, ON
K1Y 4E9

Dear Dr. Al Reesi:

Re: Protocol # 2007857-01H **Sickle Cell Disease in the Emergency Department, A Prospective Cohort Study**

Protocol approval valid until - **Tuesday, April 07, 2009**

Thank you for your e-mail dated April 7, 2008. I am pleased to inform you that this protocol underwent expedited review by the Ottawa Hospital Research Ethics Board (OHREB) and is approved. No changes, amendments or addenda may be made to the protocol or the consent form without the OHREB's review and approval.

If the study is to continue beyond the expiry date noted above, a Renewal Form should be submitted to the OHREB approximately six weeks prior to the current expiry date. If the study has been completed by this date, a Termination Report should be submitted.

The Ottawa Hospital Research Ethics Board is constituted in accordance with, and operates in compliance with the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; Health Canada Good Clinical Practice: Consolidated Guideline; Part C Division 5 of the Food and Drug Regulations of Health Canada; and the provisions of the Ontario Health Information Protection Act 2004 and its applicable Regulations.

Yours sincerely,

Raphael Saginur, M.D.
Chairman
Ottawa Hospital Research Ethics Board