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Original Research Article

Study of clinical presentation and factors affecting the outcome of acute chest syndrome in sickle cell disease

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Abstract

Background: Acute chest syndrome (ACS) is a frequent and potentially severe pulmonary illness in sickle cell disease (SCD) and it is a leading cause of death and hospitalization among patients with SCD. Aim of the present research was to study the clinical profile, predictors and outcomes of ACS in sickle cell patients.
Method: It was a cross sectional hospital based observational study enrolled total 226 admitted patients of SCD with age more than 12 years. Data on presenting signs and symptoms, laboratory findings, predictors of mortality and outcomes were recorded.
Results: Among the total 226 patients of SCD, 82 (36%) patients were diagnosed to have ACS. Joint pain (72 patients), chest pain (68 patients) and fever (55 patients) were the most common presenting symptoms. Out of 82 patients, 24 (29%) died and 58 (71%) survived. Thus the mortality rate of the study was 29%. The predictors of mortality were respiratory failure; septicemia, multi organ failure and SOFA score >10. Patients with severe anaemia, leucocytosis or leucopenia, thrombocytopenia, raised billirubin or elevated liver enzymes, deranged creatinine and hypotension were associated with poor outcome. Blood transfusion was given to 56 patients while oral hydroxyurea was given to 30 patients in the dose of 5 mg/kg.
Conclusion: A multidisciplinary approach to the management of patients of ACS is needed to improve outcome in ACS in SCD. A national consensus guideline should be performed regarding various complications of SCD including ACS.
Keywords: Acute chest syndrome, Sickle cell disease, Predictors, Mortality, Leucocytosis, Thrombocytopenia, Septicemia.

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1. Introduction

Acute chest syndrome (ACS) is a major complication of sickle cell disease (SCD) and second most common cause of hospitalization in patients with SCD. Acute chest syndrome (ACS) is defined as an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on chest X-ray [1,2]. This definition encompasses cases both where an infective organism is isolated and where no infective cause is identified. Approximately 50 percent of patients with SCD will have an episode of ACS during their lifetime [3], and mortality related to these episodes is four times higher in adults compared to children [4]. The diagnosis of ACS in sickle cell disease represents an important challenge to the physician. It may present insidiously and non-specifically, often complicating other conditions. Repeated events have been associated with an increased risk of chronic lung disease and early death [3,5,6].

However, both infectious and noninfectious etiologies including in-farction and fat embolism have been described [1, 7-10], but their frequency and clinical course are unknown [7, 9-11]. Targeting intervention appropriately is difficult due to the inability to identify high-risk patients early in the course of disease. Recent reports suggest the clinical presentation of ACS maybe predictive of etiology and severity [7]. Limited studies have found conflicting clinical pictures and suggest aggressive interventions may not be necessary for all patients [1,10]. Also, patient and

hospital level predictors of mortality in acute chest syndrome in sickle cell disease adult patients are lacking. As such, identification of risk factors can help assess prognosis and devise preventive strategies to optimize outcomes.

Therefore present research was undertaken to study the clinical profile, predictors of mortality and outcomes of ACS in sickle cell patients.

2. Materials and Methods

After obtaining written inform consent of relatives of the patients, this cross sectional hospital based observational study was conducted in the Department of Medicine, at Government Medical College, Nagpur for the period of one year. Total 226 admitted patients of age >12 years and who were known to be or freshly detected to have SCD and who satisfied the diagnostic criteria of ACS were included in the study. Patients with age <12 years, patient with haemoglobinopathies other than SCD and with past history of pulmonary diseases were excluded from the study. The diagnosis of SCD was done by RBC morphology on peripheral smear and confirmed by sickling test and hemoglobin electrophoresis. Chest x-rays, complete blood counts, were performed on admission, or when the chest symptoms developed during the course of illness. Data on presenting signs and symptoms, laboratory findings, predictors and outcomes of ACS were recorded and statistically analyzed. The p value <0.05 was considered as statistically significant and p value <0.01 was considered as statistically highly significant.

3. Observations and Results

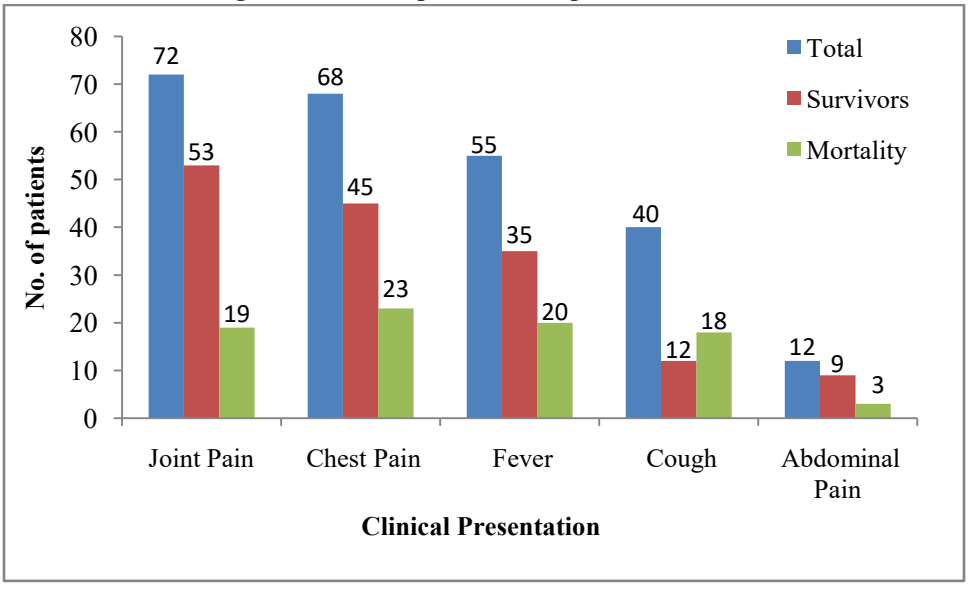
Total 226 patients of SCD were admitted during the period of one year, of which 82 (36%) patients were diagnosed to have acute chest syndrome, among them 24 (29%) died and 58 (71%) survived. Thus the mortality rate of the study was 29%. The young patients of age group between 21-40 years were commonly involved with female predominance [44 (53.65%)]. Among the ACS patients, 62 had SS pattern out of them 40 survived and 22 died while 20 had AS pattern among them 18 survived and 2 died (Table 1).

Table 1: Distribution of age, sex and sickle cell pattern in ACS patients

Age (Years)	Total ACS	Survivors	Mortality
14-20	6	2	4
21-40	63	51	12
>40	13	5	8
Sex	**Total ACS**	**Survivors**	**Mortality**
Male	38	29	9
Female	44	29	15
Pattern	**Total ACS**	**Survivors**	**Mortality**
SS Pattern	62	40	22
AS Pattern	20	18	2

The presenting symptoms at the time of hospitalization are shown in figure 1. The most common presenting symptoms were joint pain (72 patients), chest pain (68 patients) and fever (55 patients) while less common symptoms were cough and abdominal pain.

Figure 1: Clinical profile of the patients



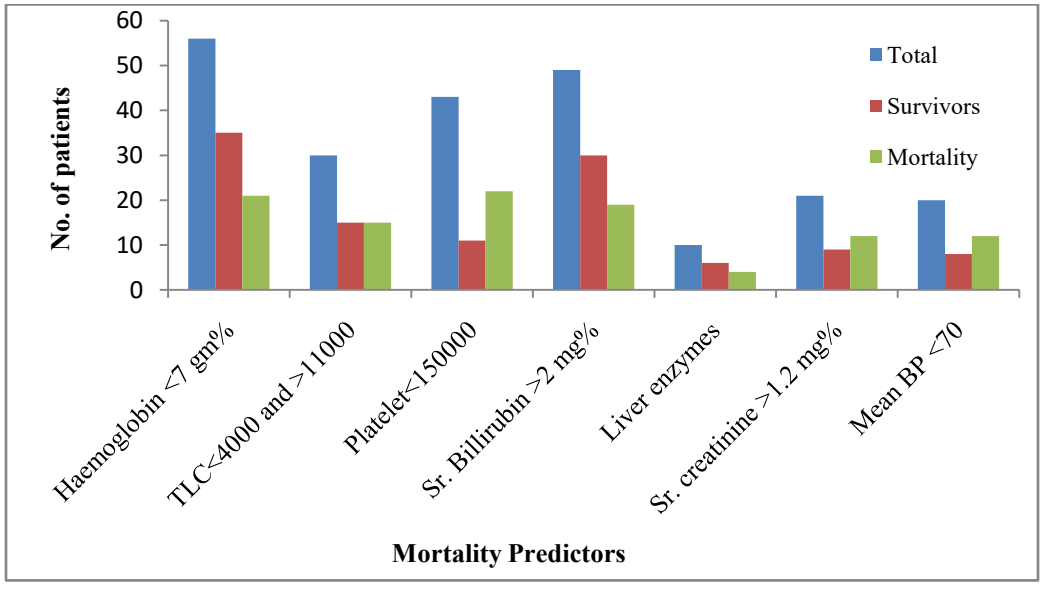
During hospitalization, multilobar involvement, especially of the lower lobes, was common in most of the patients (53 patients). Patients with bilateral haziness and lower lobe involvement had more mortality and both of them were highly significant (Table 2).

Table 2: Chest X-ray examination

Chest X-ray	Total ACS	Survivors	Mortality	P value
b/l hazy	19	6	13	p<0.01
u/l hazy	63	52	11	
Lobe	**Total ACS**	**Survivors**	**Mortality**	
Lower lobe	53	38	15	P=0.05
Upper lobe	21	17	4	-
Upper + lower lobe	8	3	5	p<0.01

Seven mortality factors were to be monitored in current study because it has impact on mortality and outcome of patients as shown in figure 2.

Figure 2: Mortality predictors of ACS patients



Other mortality predictors were depicted in table 3. The patients with PaO2/FiO2 ratio <200 have acute lung injury and had higher mortality as compared to patients with PaO_2/FiO_2 ratio >200, they have ARDS. Thirty six patients required mechanical ventilation, of which 16 survived and 20 died while 46 patients did not require ventilation of which 42 survived and 4 died, the difference in the mortality rate was highly significant. Patients of ACS having respiratory failure, septicemia, multiorgan failure (MOF) and SOFA score >10 had high mortality rate, (Table 3).

Table 3: Other mortality predictors

Predictors	Total ACS	Survivors	Mortality	
PaO2/FiO2 <200	25	10	15	p<0.01
PaO2/FiO2 >200	57	48	09	
On ventilator	36	16	20	P<0.01
Not ventilator	46	42	04	
With septicemia	49	30	19	P=0.02
Without septicemia	33	28	05	
MOF	30	14	16	P<0.001
Without MOF	52	44	8	
SOFA Score >10	25	07	18	P<0.01
SOFA Score <10	57	51	6	

The blood transfusion was given to 56 ACS patients among them 49 survived and 7 died while transfusion was not given to 26 patients, of which 9 survived and 17 patients died, blood could not be arranged. 30 patients were already receiving oral hydroxyurea in the dose of 5 mg/kg, out of which 24 patients survived and 6 patients died while 52 patients were not on hydroxyurea of which 34 survived and 18 died. The difference in the mortality was statistically highly significant.

4. Discussion

ACS is unique to SCD but in some cases it may appear to be similar to bacterial pneumonia in a patient without SCD. ACS may have a severe clinical course and can progress rapidly from mild hypoxia to respiratory failure and death. The presence of hypoxia is not included in the definition, but in clinical practice, hypoxia is a useful predictor of severity and outcome [4]. Historically, ACS is one of the most common causes of death in patients with

SCD [6,12], although mortality is improving with improved medical management [13]. ACS can also be associated with significant morbidity, including long-term parenchymal lung damage, pulmonary vascular abnormality and neurological sequelae. Patients may present to hospital acutely unwell with ACS or ACS may develop during a hospital admission following a painful crisis or post-operatively [14]. A recent study of the effect of hospital type and provider specialty on outcomes of hospitalized adolescents and young adults (16–25 years) with sickle cell disease and acute chest syndrome found that general hospitals carry higher intubation risks for adolescents and young adults with SCD and ACS compared with children's hospitals. A Vaso-occlusive crisis (VOC) is the main cause of SCD-patient Emergency-Department arrival and ACS is one of its most severe complications, especially in adults, with high morbidity and mortality [3, 6, 15-17].

In present study, the incidence of ACS was 36% (82 patients out of 226) which indicating a high prevalence of ACS in admitted patients of SCD. Out of 82 patients, 20 were not having clinical features of ACS at the time of admission but they developed ACS 2-3 days after hospital stay, so patients admitted to hospital for painful crisis should be considered to be in the prodromal phase of ACS and monitored closely. 50% of patients of ACS initially admitted as patients of vaso-occlusive crises (VOC) and average time to develop ACS was 2.5 days, this finding was similar to the study done by Vichinsky *et al* [18]. The young patients of age between 21-40 years were commonly involved and having higher mortality and poor outcome. Female predominance was observed in the study, this may be because of females are more anaemic and have poor immunological status. Consistent with prior studies [16,19], current study showed that adults with Hb-SS phenotype accounted for the highest rate of acute chest syndrome hospitalizations.

Patients with Hb-SS pattern had significantly higher mortality as compared to Hb-AS pattern, this finding was correlated with the study done by Platt *et al* [6]. Neither the in-hospital mortality nor the length of stay was influenced by the genotype of sickle cell disease. This could suggest that, rather than the genotype, it is the severity of acute chest syndrome and resulting respiratory failure (as evidenced by the need of mechanical ventilation) that influences mortality.

The patients presenting with chest pain, fever and cough were noted to have higher mortality, $p<0.01$. Chest radiograph remains the corner stone diagnostic test for ACS, so patients getting admitted for VOC, should benefit from chest radiogram for early detection of ACS. As sometimes, clinical assessment is insufficient in diagnosing early cases of ACS. Chest x-ray is one of the most commonly available bed side investigations and almost always involves the lower lobes. ACS in adults was characterized by severe pain and lower or multilobe disease and implies that vascular occlusion is a common cause of ACS in adults. The radiographic findings of pre-dominantly lower lobe disease corresponds to autopsy results demonstrating pulmonary thrombosis and fat embolism [20,21]. The finding of both pain and lower lobe disease in patients suggests chest wall infarction may also be a common cause of ACS and is compatible with the clinical picture reported in the study by Bellet [11]. Bronchoscopy is more sensitive method in determining etiology and in the one adult study to use bronchoalveolar lavage, 20% of all episodes were bacterial [22].

Respiratory failure, septicemia, multiorgan failure (MOF) and SOFA score >10 was the most common cause of death in current study which was correlated with the study done by Platt *et al* [6].The impact of the need for mechanical ventilation on outcomes in adult patients with sickle cell disease and respiratory failure due to acute chest syndrome is unknown. Thirty patients had MOF which include renal disease (KFT) (21 patients), hepatic failure (10), shock (20) and septicemia in 30 patients. Other causes of death in ACS patients included severe anaemia, leucocytosis or leucopenia, thrombocytopenia, raised billirubin or elevated liver enzymes, deranged creatinine and hypotension and which were associated with poor outcome. The mortality rates in ACS will be dependent in part on the appropriateness of medical management. Even with good medical treatment, overall mortality rates of up to 3% are reported, with the overall death rate in adults being four times higher than in children [4].

For many patients, treatment for ACS is mostly supportive. Early detection and supportive treatment may limit its severity and prevent death. Treatment includes continuous pulse oximetry and delivery of supplemental oxygen to patients with hypoxemia, adequate pain management, empiric antimicrobial therapy, monitoring of the hemoglobin concentration, blood transfusion, and maintenance of good hydration [22]. Two treatment aspects were of particular interest in this study i.e. oral hydroxyurea and blood transfusion. Simple blood transfusion may be beneficial in shortening the clinical course and decreasing mortality [23,24]. The use of blood transfusion in 68.29% patients in current study may have contributed to rapid improvement of our patients. Mortality and morbidity rates in sickle cell disease (SCD) have been considerably reduced since the introduction of hydroxyurea (HU) in the 1990s [6, 20, 25].

A recent update of the Multicenter Study of Hydroxyurea (MSH) showed that at 9 years' follow-up, the mortality rate among patients who take HU is reduced 40% compared with the rate among patients who do not take the drug [26]. As previously reported [6, 20] ACS remains the major cause of death among patients on hydroxyurea (35%). Similarly, in present study also 25% of death was seen among ACS patients on hydroxyurea.

5. Conclusion

Multidisciplinary approach to the management of patients of ACS in the form of blood transfusion, antibiotic therapy, hydroxyurea, bronchodialators, hydration, spirometry and mechanical ventilation is needed to improve outcome in acute chest syndrome in sickle cell disease. There should be high index of suspicion of ACS in patients admitted with VOC. Prompt and serial radiological investigations will confirm the diagnosis of ACS. Also the increased hospital resource utilization and early identification of risk factors may enable optimization of outcomes. A national consensus guideline should be formed regarding various complications of sickle cell disease including ACS.

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