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Clinical Characteristics and Outcome of Patients with Sickle Cell Disease Admitted to the Medical Intensive Care Unit

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Abstract: *Sickle cell disease (SCD) is the most prevalent genetic blood disorder in the United States. There is very limited information on patients with SCD in the intensive care setting. We identified 108 unique patients with SCD, 18years and older, who were admitted to the MICU of the Detroit Medical Center from January 1st 2006 through December 31st 2012.*

Majority (80%) had homozygous sickle cell disease (SS). Commonest primary diagnosis for admission into the MICU was acute chest syndrome (25%) followed by sepsis (13%). The median duration of MICU stay was 3 days with a range of 1 to 40 days. Mortality on MICU discharge was 12.9% which is lower compared to older studies from UK and Oman that reported a mortality of around 19% and 16% respectively. Although several variables were significantly associated with death on MICU discharge, only ventilator support remained significant on multi-variable logistic regression analysis.

Although retrospective, the study reviewed relatively large number of patients admitted to theMICU. The relatively low mortality of these patients may reflect improved overall ICU care, lung protective ventilatory strategies, better treatment of sepsis and multidisciplinary approach to the management of these patients. A prospective, multi-center study is recommended.

Keywords: *Sickle cell disease, Mortality, Intensive Care unit*

1. Introduction

Sickle cell disease (SCD) is the most prevalent genetic blood disorder in the United States with 2 million carriers of the sickle cell gene (heterozygous state) and approximately 72,000 with sickle cell disease (homozygous state). The disease is most common among African Americans where 1 out of 500 newborns have SCD.(1)

A single point mutation in the ®-globin gene from Val^6 to Glu^6 results in the formation of sickle cell hemoglobin. Homozygous sickle cell disease (Hb-SS) is the most common variant and also the most severe form of SCD.(2)

The manifestations of SCD are variable and include hemolysis, inflammation and vasso-occlusion leading to acute and chronic tissue ischemia and organ dysfunction. Some of the manifestations of SCD, particularly acute chest syndrome, are severe and usually require MICU admission. In addition, patients with sickle cell disease can be admitted to MICU from illnesses which are not directly related to sickle cell. However the outcome is likely affected by their underlying SCD.(2, 3)

There are an estimated 4 million medical intensive care unit (MICU) admissions per year in the United States, with an average mortality of 8-19%. (4, 5) Although heterogeneous populations of patients are cared for in the MICU, many of the diseases are well studied. Unfortunately, Sickle Cell Disease has not been studied as well in the intensive care setting with very little data in the scientific literature. As sickle cell disease patients live longer with better supportive therapy, it is reasonable to presume that their rates of admission to the intensive care units will increase. The aim of the study was to describe the clinical characteristics and outcome of sickle cell patients admitted to the MICU.

2. Subjects and Methods

After obtaining IRB approval, billing codes were used to identify patients 18 years and older

with sickle cell disease admitted to the medical intensive care unit of the Detroit Medical Center from January 1st 2006 through December 31st 2012. Only patients with homozygous sickle cell disease (SS), Sickle C disease (SC) and Sickle β^0/β^+ thalassemia($S\beta^0/S\beta^+$) confirmed by hemoglobin evaluation were included in the study. In cases of multiple admissions, only the first admission was used.

Data were collected from the electronic medical record (EMR) on baseline characteristics, reason for admission to the MICU, selected clinical and laboratory parameters and, therapeutic interventions during MICU stay. The primary outcomes of interest were collected from EMR: survival status upon discharge from MICU and survival status on day 28 post-MICU admission. Baseline laboratory values were collected from the most recent outpatient visit prior to admission to the MICU.

3. STATISTICAL METHODS

Categorical variables were associated with binary survival status upon discharge from MICU and on day 28 post-MICU admission using a chi-squared test or Fisher's exact test, where appropriate; while t-test was used to associate continuous variables with these outcomes. For each outcome, univariable logistic regression was used to calculate odds ratios for each predictor variable and multivariable logistic regression was used to identify a parsimonious set of predictor variables. Fisher exact test was used for the exploratory analysis to look for association between APACHE (acute physiology and chronic health evaluation) II and SOFA (sequential organ failure assessment score) scores with survival status upon discharge from the MICU.

4. RESULTS

A total of 108 unique patients with sickle cell disease were admitted to the MICU of the DMC from Jan 1st 2006 to Dec 31st 2012. Of these majority (80%) had homozygous sickle cell disease (SS). Commonest primary diagnosis for admission into the MICU was acute chest syndrome in 27 patients (25%) followed by sepsis in 14 (13%). The most common co-morbidity was hypertension.

The median age was 34.5 years with a male to female ratio of 0.9. The median duration of MICU stay was 3 days with a range of 1 to 40 days. (Table 1)

Table1. *Clinical characteristics of study subjects.*

Variable	Number (%)	Median (with range)
Genotype:		
Hb SS	87 (80.5)	
Hb SC	13 (12.1)	
Hb $S\beta^0$ /Hb $S\beta^+$	6 (5.6)	
Missing information	2 (1.8)	
Age (years)		34.5 (18-74)
Gender:		
Male	52 (48)	
Female	56 (52)	
Diagnosis on admission to the ICU:		
Acute chest syndrome	27 (25)	
Sepsis	14 (13)	
Respiratory failure	13 (12)	
Altered mental status	10 (9.3)	
CVA	7 (6.4)	
Cardiac arrest	4 (3.7)	
Others*	33 (30.6)	
Duration of stay in ICU(days)		3 (1-40)
Mechanical ventilation	32(29)	
Vasopressors	18(17)	
Renal replacement therapy	7(6)	
Mortality on:		
MICU discharge	14(12.9)	
Day 28	15(14)	

**Others include arrhythmias, electrolyte abnormalities, hypotension, hypertensive emergency, NSTEMI, Seizure, hematemesis, toxic epidermal necrolysis etc…*

Thirty-two patients (29%) were intubated at some time during their MICU stay. The median duration on the ventilator was 3 days with a range of 1 to 30 days. Eighteen (17%) of patients were on one or more vasopressors and seven (6%) of patients, who were not on chronic hemodialysis, started renal replacement therapy at some point during their MICU stay. Thirty-six patients (33%) had red cell exchange transfusion at some point in their MICU stay.

Mortality on MICU discharge was 12.9% (14 out of 108 patients). Day 28 mortality was similar at 14% (15/106 patients). Information on day 28 status was not available for two patients. All 14 patients who died in the MICU were intubated. Similarly all but one patient who died on day 28 were intubated. However, 18 patients who were intubated at some point in their MICU stay were alive on discharge from the MICU and on day 28.

Of all the variables tested only arterial blood gas PH (<7.2) in the first 24hours of MICU admission, hemodialysis support, duration of MICU stay, vasopressor use and ventilator support were significantly associated with death on MICU discharge. However, only ventilator support remained significant on multi-variable logistic regression analysis. The same was true for day 28. (Table 2)

Table2. *Association of variables on outcome at MICU discharge.*

Variable**	Levels	Alive	Expired	P- value
gender				0.663
	F	50(0.53)	6(0.43)	
	M	44(0.47)	8(0.57)	
genotype				0.718
	SB+	3(0.03)	0(0.00)	
	SB0	3(0.03)	0(0.00)	
	SC	10(0.11)	3(0.23)	
	SS	77(0.83)	10(0.77)	
MICU stay(days)				0.013
	(0,6]	75(0.83)	8(0.57)	
	(6,14]	11(0.12)	2(0.14)	
	(14,100]	4(0.04)	4(0.29)	
Vasopressor				<0.001
	no	85(0.91)	4(0.29)	
	yes	8(0.09)	10(0.71)	
Intubated				<0.001
	No	76(0.81)	0(0.00)	
	Yes	18(0.19)	14(1.00)	
HD/CRRT[#]				0.044
	no	81(0.86)	10(0.77)	
	yes	4(0.04)	3(0.23)	
	chronic HD	9(0.10)	0(0.00)	
Red cell exchange				0.770
	no	62(0.66)	10(0.71)	
	yes	32(0.34)	4(0.29)	
NIPPV[$]				1.000
	no	80(0.86)	12(0.86)	
	yes	13(0.14)	2(0.14)	
PH*				0.002
	≥7.2	55(0.89)	6(0.46)	
	<7.2	7(0.11)	7(0.54)	

**PH: In case of multiple PH values for the same patient, the worst value was used.*

*[#]HD: hemodialysis. CRRT: continuous renal replacement therapy. $NIPPV: noninvasive positive pressure ventilation. ** Numbers may not add up to 108 due to missing information/missing variables.*

A separate comparison was made for those 32 patients who were intubated at some point during their MICU stay with respect to their outcome at MICU discharge. There was no significant association with death phenotype for all the tested variables. (Table 3)

Table3. *Association of variables with outcome on MICU discharge for intubated patients (n=32).*

Variable**	Levels	Alive	Expired	P-value
gender				0.503
	F	11(0.61)	6(0.43)	
	M	7(0.39)	8(0.57)	
genotype				0.447
	SB+	0(0.00)	0(0.00)	
	SB0	2(0.12)	0(0.00)	
	SC	2(0.12)	3(0.23)	
	SS	13(0.76)	10(0.77)	
vasopressor				0.186
	no	10(0.59)	4(0.29)	
	yes	7(0.41)	10(0.71)	
HD/CRRT				0.625
	no	16(0.89)	10(0.77)	
	yes	2(0.11)	3(0.23)	
	chronic HD	0(0.00)	0(0.00)	
Red cell exchange				1.000
	no	13(0.72)	10(0.71)	
	yes	5(0.28)	4(0.29)	
NIPPV				0.664
	no	13(0.76)	12(0.86)	
	yes	4(0.24)	2(0.14)	
PH				0.273
	≥7.2	13(0.72)	6(0.46)	
	<7.2	5(0.28)	7(0.54)	
Intubated Within 24hrs				0.694
	no	7(0.39)	3(0.25)	
	yes	11(0.61)	9(0.75)	

*** Numbers may not add up to 32 due to missing information/missing variables.*

Exploratory analysis was done for the few admissions with sufficient information to calculate APACHE II (42 admissions) and SOFA (32 admissions) scores. The mean APACHE II score was 21with a standard deviation of 7.7. There was statistically significant association between APACHE II score of >25 and death on MICU discharge (P=0.008, OR: 13.98[1.43, 713.46]). The mean SOFA score was 7 with standard deviation of 2.7. There was no statistically significant association between SOFA score and death on MICU discharge (P=0.39, OR: 2.47[0.29, 32.12]).

5. DISCUSSION

The study reviewed relatively large number of patients with SCD requiring admission to the MICU. It showed lower ICU mortality (12.9%) for adult sickle cell patients compared to older studies from UK and Oman that reported a mortality of around 19% and 16% respectively. (6, 7) ICU mortality for pediatric sickle cell patients was shown to be even lower at 6% in another study from the UK.(8) The relatively low mortality of these patients may reflect improved overall ICU care, lung protective ventilatory strategies, better treatment of sepsis and multidisciplinary approach to the management of these patients. Of all the variables tested, only mechanical ventilation remained significantly associated with death phenotype on multi-variable analysis in this study (table 2). Similar observation was made from the UK study where none of the patients who did not require ventilation support died. Another study from Oman showed that the need for inotropic support and mechanical ventilation were good predictors of mortality.(6, 7) This is not surprising as almost every patient admitted to the ICU will be on ventilator support prior to death. A separate analysis was made to look for differences between patients who were intubated and deceased versus those who were intubated and discharged alive from MICU. None of the variables tested including the timing of intubation (within 24 hours of MICU admission or later), additional organ support, and genotype showed statistically significant difference between the two groups likely due to few numbers of events. (Table 3)

Similar to other studies, acute chest syndrome was the commonest diagnosis for MICU admission in this study.(6, 8) It is probably underestimated as most of the patients given the diagnosis of respiratory failure may actually have acute chest syndrome. The mortality on MICU discharge for patients with a diagnosis of acute chest syndrome was around 7%. This is similar to the mortality reported in a large prospective study on outcomes of acute chest syndrome in the US, which reported a mortality of around 9% in patients aged 20 years or more. (9) In a pediatric study from the UK, none of the patients admitted to the ICU with acute chest syndrome died suggesting very low mortality for acute chest syndrome in the pediatric age group. (8)

The association between APACHE II and SOFA score in the few admissions was only exploratory due to missing data for several patients. In addition, the wide confidence interval makes interpretation and relevance a challenge. The predictive value of SOFA score could also be affected by elevated bilirubin (from hemolysis) and lower creatinine (from hyper filtration) in most patients with SCD, both of which are components of the sore. On the other hand, both APACHE and SOFA were found to be useful in predicting ICU outcomes in several studies unrelated to SCD.(10-12) Future prospective studies will be helpful as there are no previous studies on the utility of APCHE and SOFA scores in predicting outcome for patients with SCD.

The study has several limitations including its retrospective design; inadequate number of events for robust statistical analysis and missing data. A prospective, multicenter study is recommended.

In summary, this study represents the largest number of adult SCD patients admitted to the MICU. It shows that the MICU and 28 day mortality rate for these patients is relatively low and that mechanical ventilation is predictor of poor outcome.

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