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Renal Failure in Sickle Cell Disease: Prevalence, Predictors of Disease, Mortality and Effect on Length of Hospital Stay

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Abstract

Renal dysfunction in sickle cell disease is not only a chronic comorbidity but also a mortality risk factor. Though renal dysfunction starts early in life in sickle cell patients, the predictors that can identify sickle cell disease patients at risk for developing renal dysfunction is not known. We used the Truven Health MarketScan Medicaid Databases from 2007–2012. Incidence of new acute renal failure (ARF) and chronic kidney disease (CKD) was calculated in this cohort. There were 9481 patients with a diagnosis of sickle cell disease accounting for 64,201 hospital admissions, during the study period. Both ARF and CKD were associated with higher risk of inpatient mortality, longer duration of the hospital stay and expensive hospitalizations. The yearly incidence of new ARF in sickle cell disease patients was 1.4% and annual CKD incidence was 1.3%. The annual rate of new ARF and CKD in the control group was 0.4 and 0.6%, respectively. The most important predictors of new CKD were proteinuria, ARF and hypertension. Chronic kidney disease, hypertension and sickle cell crisis were the most important predictors of new ARF. The annual rate of incidences of ARF and CKD were 2- to 3-fold higher in sickle cell disease compared to the non sickle cell disease group. Besides the common risk factors for renal disease in the general population, it is imperative to monitor the sickle cell disease patients with more severe disease to prevent them from developing renal dysfunction.

Keywords

Administrative database; length of hospital stay; mortality; renal failure; sickle cell disease

Introduction

Sickle cell disease is a genetic disorder of hemoglobin (Hb) which disproportionately affects persons of African and to a lesser extent, Hispanic descent [1]. On the molecular level, it is

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characterized by the inheritance of a mutated Hb gene, Hb S (*HBB*: c.20A>T) along with or without any other abnormal Hb gene. Clinically, the manifestations of sickle cell disease are protean, but the general underlying pathology is the polymerization of Hb S in hypoxic conditions, leading to deformability of red blood cells (RBCs), hemolysis and occlusion of microvasculature.

With the significant advances in prophylactic and therapeutic approaches in the management of sickle cell disease, there has been some improved survival among children with sickle cell disease, with the majority of children attaining adulthood [2,3]. However, the Cooperative Study of Sickle Cell Disease from 1978–1988 reported a median age at death of 42 years in males and 48 years for females [4]. The analysis of the Centers for Disease Control (CDC) Compressed Mortality Report in 2006 showed a median age at death of 39 years with only 35.0% surviving beyond age 35 years, and also age-specific death rates in the transitioning adults as well as the 45 to 74-year-old age group seeing an increase in 1999–2009 compared to before, which are less encouraging [1,3]. Additionally, there has not been any steady decrease of hospitalization rates noted from 1998 to 2008 in sickle cell disease admissions, with only a slight decrease in length of hospital stay of 5.38 days in 1998 to 5.18 days in 2008 [5].

In light of these outcomes, which still persist despite advancement in medical care, it is imperative to investigate individual patient factors that underlie these adverse events. One may postulate that with an aging population of patients with sickle cell disease, the coexistence of chronic illnesses, adds to the complexity of managing the disease and may influence the outcomes. Indeed, sickle cell nephropathy though not fully elucidated, is one of the leading causes of mortality in patients with sickle cell disease [3,4]. Renal dysfunction starts early in life in patients with sickle cell disease [6]. In childhood, the predominant feature is hyposthenuria due to impaired concentrating ability of the proximal tubule, this manifest as nocturia and enuresis. In adolescence, erythrocyte sickling in the medullary vessels leads to renal ischemia, hematuria and proteinuria with compensatory vasodilation and resulting hyper filtration evidenced by increased glomerular filtration rate (GFR) [7]. Eventually this increased GFR combined with glomerular hypertrophy results in glomerulosclerosis, and progresses to reduced GFR, chronic kidney disease (CKD) and end-stage renal disease in the adult years [8,9].

Knowledge of the natural progression of the disease, as well as identification of persons at-risk or early in their disease, allows for timely intervention and improved outcomes [10]. This study sought to assess the prevalence of renal disease [acute renal failure (ARF) and CKD] in sickle cell disease across all age groups in a US population and to identify the patient characteristics that predict the development of renal disease. Additionally, the effect of renal disease on various outcomes in sickle cell disease admissions such as length of hospital stay and mortality was also assessed.

Materials and methods

A retrospective review of public data recorded in the Truven Health MarketScan® Medicaid Databases (<http://truvenhealth.com/your-healthcare-focus/analytic-research/marketscan->

research-databases) was performed. The MarketScan[®] Medicaid Database contains the medical, surgical, and prescription drug experience of 13 million Medicaid enrollees from multiple states. It includes records of inpatient services, inpatient admissions, outpatient services, and prescription drug claims, as well as information on long-term care and other medical care.

Patients discharged from participating hospitals with a diagnosis of sickle cell disease from 2007–2012 were included in the study. The sickle cell disease diagnosis was defined based on ICD-9 codes. We also used ICD-9 codes to define chronic and acute renal disease as well as to identify any inpatient procedures. In each hospital admission the following outcomes were evaluated: mortality, length of hospital stays and total payment.

We used two different units for data analysis. Discharge data: adult discharge data was analyzed using generalized estimation equations (GEE) adjusted for repeated admission for each patient. In each analysis, the odds ratio (OR) and 95% confidence interval (95% CI) of different clinical and demographic variables and having chronic renal disease or ARF in discharge claim were computed in separate models. We also assessed the relationship between renal disease diagnosis, inpatient mortality, duration of hospital stays and total number of hospital admissions for the same study period by GEE models.

For each adult patient with and without a sickle cell disease diagnosis, the rate of new CKD and ARF was calculated for the study period using inpatient and outpatient records. Among the patients with a sickle cell disease diagnosis, we used logistic regression analysis to assess the predictors of new CKD and ARF. The new CKD and ARF were defined as having any of these two diagnoses in year 2012 compared to 2007. We choose predictors from year 2007 to enter in models.

Results

There were 64,201 hospital admissions with at least one sickle cell diagnosis from 2007–2012. These admissions occurred in 9481 patients with a median (interquartile range) of six (two–15) admissions for each patient. The frequency of chronic renal disease in children, adults and patients over 40 years old were 0.1, 5.0 and 15.9%, respectively. The frequency of ARF in children, adults and patients over 40 years old were 0.2, 4.0 and 11.0%, respectively. During 28.0% of these 64,201 hospital admissions, patients received blood transfusions. The median (interquartile range) length of hospital stay was 4 (2–6) days (Table 1).

On further evaluation, male gender, presence of proteinuria, diabetes, hypertension, dyslipidemia, chronic heart disease and transfusion were found to be the risk factors for CKD. Chronic renal disease was seen in 68.0% of admissions with hypertension and 25.0% of admissions with heart failure (Table 2).

Male gender, presence of proteinuria, diabetes, hypertension, chronic heart disease and transfusion were found to be risk factors for ARF. Acute renal failure was seen in 41.0% of admissions with hypertension and 25.0% of admissions with heart failure (Table 3).

Both CKD and ARF were associated with higher risk of inpatient mortality, longer duration of hospital stays and higher admission charges. Relative risk of inpatient mortality was more than doubled during admissions with ARF than with CKD and mean increase in hospital stay was also greater in admissions with ARF compared with CKD (Table 4).

We further investigated the inpatient and outpatient diagnosis in the 6-year period of study and found 13,127 adult patients with at least one diagnosis of sickle cell disease in patient records and 21,205 patients with no record of sickle cell disease. The incidence rate of new ARF and CKD in sickle cell disease patient was 6.8% (annual rate of 1.4%) and for CKD it was 6.7% (annual rate of 1.3%) during the study period. Whereas the annual rate of ARF and CKD in control patients was 0.4 and 0.6%, respectively. Furthermore, we assessed the clinical event of 2007 among which can predict the new CKD or ARF in sickle cell disease at 2012 in a logistic regression analysis. The predictors of new CRF were found to be male gender, older age, having proteinuria, ARF, hypertension, diabetes, blood transfusion (in 2007) and predictors of new ARF were found to be male gender, older age, having proteinuria, ARF, hypertension (in 2007) (Table 5b).

Discussion

Renal dysfunction is a common comorbidity in patients with sickle cell disease, and more so in the adult subset of patients [11,12]. In our study we found the prevalence of CKD in adults with sickle cell disease was 5.0% and ARF was 4.0%, and incidence of both almost tripled compared to adults without sickle cell disease. Both CKD and ARF conditions were associated with higher mortality and health care utilization in this study.

Similarly, in a prospective trial that enrolled 725 patients with sickle cell disease, 4.2% developed renal failure, with a median survival of 4 years and median age at diagnosis of 23 years [13]. When these patients were evaluated in a follow-up study, and an additional 1056 patients were enrolled, the incidence of renal failure increased to 12.0%, with a median age at diagnosis of 37 years [11]. The mean age at enrollment in this follow-up study was 20 years and the patients were then followed for an additional 15 years, causing the study population to be older than that of the preliminary study. This draws a parallel to our study in that increasing age was associated with an increased incidence of renal failure. In another prospective study in 300 adult patients followed at a sickle cell disease clinic, the prevalence of renal dysfunction was found in 21.0% of patients with genotype Hb SS. Of these patients, 29.0% had CKD stage 3 or higher [13].

In our study of patients with sickle cell disease, the incidence of ARF and CKD over the 6-year period was 2–3 times higher in sickle cell disease patients compared to non sickle cell disease patients. Although overall trends suggest increased prevalence and incidence of renal failure in patients with sickle cell disease, there was a wide variation in the actual figures among the various studies as reported above [11–13]. This is likely due to varying definitions used to define renal failure, and different equations used to measure the GFR or creatinine clearance, coupled with the unreliable measurement of creatinine clearance in patients with sickle cell disease. These inherent variations may over- or underestimate the true prevalence of renal dysfunction patient population.

In our study, after adjusting for age, both ARF and CKD were associated with increased mortality during hospital admission. There was a 3.6 relative risk (RR) for death on admission with CKD (95% CI: 2.6–5.0) and an even higher 9.5 RR for death on admission with ARF. Similarly, survival in patients with sickle cell disease was decreased in the presence of renal disease and it was found to be a risk factor for mortality [13]. Platt *et al.* [4] reported 18.0% mortality in sickle cell disease patients with organ dysfunction such as renal failure, and renal dysfunction was also the cause of death in 16.4% of patients as reported by Hamideh and Alvarez [3]. Another study in sickle cell disease patients over a period of 5 years with 105 patients and 189 admissions reported a mortality rate of 38.0% [14]. It can thus be deduced that the combination of sickle cell disease and renal failure results in worse outcomes than when these diseases occur alone.

The length of a hospital stay in patients with sickle cell disease has been studied in various age and socioeconomic groups with varying underlying causes for hospitalization [15–17]. Our study examined the impact of a diagnosis of CKD or ARF in patients with sickle cell disease on the length of hospital stay. The results demonstrated that after adjusting for age, patients with sickle cell disease who were diagnosed with CKD had a 1.6-day increase in hospital stay and in those with ARF the hospital stay was lengthened by 3.2 days. The issue of length of hospitalization of patients with sickle cell disease is one of great relevance in the era of cost conscious care as the chronicity of the condition and care involved in managing this condition adds to a high economic burden [18–20]. From the analysis using MarketScan® Medicaid and Commercial Claims databases for 2005 of the children with and without sickle cell disease, the medical expenditure was noted to be six to 11 times higher [18]. It was also estimated to amount to US\$7393,600 for a life care plan of sickle cell disease patients 19–50 years old with a 50-year life expectancy [19]. Also, an admission for renal failure with duration of 7 days was estimated to be US\$21,070 [19]. In our study we also noted an increase in the total admission charges for patients with renal disease that mirrored the increase in length of stay, with an excess of US\$3866 seen in patients with CKD and an excess of US\$8205 in patients with acute kidney injury (AKI).

It is now evident that age is a predictor of developing renal failure in sickle cell disease [11]. It has also been reported that hypertension, proteinuria and increased severity of anemia predicts the development of end-stage renal failure in these patients [13]. Our study drew similar conclusions with the predictors of ARF in hospital admissions being advancing age, male gender, and presence of proteinuria, diabetes, hypertension, chronic heart disease and blood transfusion. For CKD in hospitalized sickle cell disease patients, the predictors identified in our study were male gender, presence of proteinuria, diabetes, hypertension, dyslipidemia, chronic heart disease and blood transfusion. Effect of transfusion on renal function could be explained by severity of hemolysis in patients who require transfusions, iron overload or by effect of transfusion reaction on renal function [21–23], with a very low rate of transfusion reaction already reported in these patients [24].

This study helped us in identifying risk factors for development of renal failure in sickle cell disease. It is critical, as it highlights an opportunity to identify these patients early, in an effort to prevent them from developing renal dysfunction, which can eventually progress to end-stage renal disease (ESRD), decrease quality of life and increase mortality. Patients may

be offered therapeutic interventions such as hydroxyurea (HU) that has shown promising results in studies evaluating markers of renal disease in sickle cell disease patients. In the Hydroxyurea Study of Long-Term Effects (HUSTLE), patients between the ages of 4–7 years showed a statistically significant decrease in GFR (median decrease of 29.7, $p = 0.03$) after 3 years of HU therapy at the maximum tolerated dose [25]. This beneficial effect of HU was also seen in the adult sickle cell disease population, where its effect on albuminuria, an early marker for renal disease was evaluated. In a cross sectional study done by Laurin *et al.* [26], a total of 149 patients aged >18 years with sickle cell disease were evaluated. Patients receiving HU therapy had a lower prevalence of albuminuria than those who were not on HU (34.7 vs. 55.4, $p = 0.01$).

Limitations

This study had certain limitations. We studied Medicaid beneficiaries who have an increased access to health care and have a higher hospital admission rate and better self-reported health status compared to non insured individuals. We used administrative data recorded by the ICD classification that may have been influenced by the accuracy of clinical diagnoses and coding procedures. The data bases did not include detailed medical information, such as sickle genotype, pain severity score, percentage of Hb S prior to a blood transfusion or use of inpatient medications, and therefore it was not possible to control or stratify our results according to these important factors. We were not able to assess the effect of community factors such as socioeconomic status, access to medical care or type and size of hospital on outcomes.

Conclusions

The annual rate of incidence of ARF and CKD was 2- to 3-fold higher in sickle cell disease patients compared with the non sickle cell disease group. Both ARF and CKD were found to be independent predictors of increased length of hospital stay, inpatient mortality and higher admission charges. Increasing age, male gender, proteinuria, diabetes, hypertension, chronic heart disease and blood transfusions were found to be predictors of both ARF and CKD. This information can assist in early identification of at-risk patients and providing timely treatment to halt or reverse disease. Further studies are needed to evaluate the effect of these interventions on overall morbidity, cost of care and mortality in sickle cell disease patients.

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Table 1

Distribution of clinical and demographic variables of sickle cell disease hospital admissions.

Number of admissions	64,201
Age (years) (%):	
0–17	31.0
+18	69.9
Gender:	
males	43.0
females	57.0
Chronic kidney disease	4.0
Acute renal failure	3.0
Sickle cell crisis	84.0
Proteinuria	0.2
Diabetes	4.0
Hypertension	12.0
Dyslipidemia	4.0
Heart failure	0.7
Transfusion	28.0
Duration of hospital stay in days	4 (2–6)
Total hospital charges in US\$	8127 (4137–16,695)
Death	254 (0.40)

Table 2

Distribution of clinical diagnosis based on chronic renal disease in sickle cell disease hospital admissions of adults.

	Chronic Renal Disease Negative (%) n=41,823	Chronic Renal Disease Positive (%) n=2328	Unadjusted OR (95% CI)
Female gender	62.0	47.0	0.6 (0.5–0.7)
Sickle cell crisis	90.0	74.0	0.7 (0.6–0.8)
Proteinuria	0.2	1.0	2.5 (1.6–4.0)
Diabetes	4.0	10.0	1.5 (1.3–1.8)
Hypertension	13.0	68.0	3.7 (3.4–4.2)
Dyslipidemia	1.0	3.0	1.4 (1.04–1.9)
Heart failure	5.0	25.0	2.0 (1.7–2.3)
Transfusions	31.0	46.0	1.2 (1.1–1.3)

OR: odds ratio; 95% CI: 95% confidence interval.

Table 3

Distribution of clinical diagnosis based on acute renal failure in sickle cell disease hospital admissions of adults.

	Acute Renal Failure Negative (%) <i>n</i> =42,366	Acute Renal Failure Positive (%) <i>n</i> =1785	OR (95% CI)
Females gender	62.0	48.0	0.6 (0.5–0.7)
Sickle cell crisis	89.0	81.0	0.7 (0.6–0.9)
Proteinuria	0.2	1.0	2.7 (1.6–2.3)
Diabetes	5.0	9.0	1.8 (1.5–2.2)
Hypertension	15.0	41.0	2.0 (1.8–2.3)
Dyslipidemia	1.0	2.0	1.1 (0.7–1.6)
Heart failure	5.0	25.0	3.1 (2.7–3.6)
Transfusions	31.0	48.0	1.6 (1.5–1.8)

OR: odds ratio; 95% CI: 95% confidence interval.

Table 4

Outcome of hospital admissions in renal disease.

	RR for Death^a	Mean Increase in Duration of Hospital Stay (day)^a	Mean Increase in Total Admission Charges (US \$)^a
Chronic renal disease	3.6 (2.6–5.0)	1.6 (1.3–1.9)	3866 (3082–4651)
Acute renal failure	9.5 (7.1–12.6)	3.2 (2.9–3.5)	8205 (7526–8885)

RR: relative risk.

^a Adjusted for age.

Table 5

Predictors of new chronic kidney disease and acute renal failure in sickle cell disease patients, obtained from inpatient and outpatient records.

	OR (95% CI)	<i>p</i> Value
a) Chronic kidney disease (<i>n</i> = 3538)		
Females gender	0.6 (0.5–0.9)	0.005
Age (years)	1.04 (1.03–1.05)	<0.001
Proteinuria	3.1 (1.2–8.3)	0.020
Acute renal failure	3.0 (1.5–6.0)	<0.001
Hypertension	2.3 (1.7–3.2)	<0.001
Diabetes	1.8 (1.3–2.5)	0.001
Blood transfusions	1.7 (1.1–2.4)	0.008
b) Acute renal failure (<i>n</i> = 3624)		
Females gender	0.6 (0.4–0.8)	<0.001
Age (years)	1.02 (1.01–1.03)	<0.001
Sickle cell crisis	2.2 (1.7–3.0)	<0.001
Chronic kidney disease	2.0 (1.2–3.2)	0.005
Chronic heart disease	1.7 (1.2–2.5)	0.005
Hypertension	1.7 (1.2–2.3)	0.002
Diabetes	1.7 (1.2–2.4)	0.006

OR: odds ratio; 95% CI: 95% confidence interval.