Improved survival among sickle cell kidney transplant recipients in the recent era

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Keywords: kidney transplant, patient survival, sickle cell

ABSTRACT

Background. Studies from older cohorts of kidney recipients have observed that recipients with sickle cell disease (SCD) have lower patient survival compared with age- and race-matched controls. We examined whether survival has improved among SCD recipients in the current era.

Methods. Using Organ Procurement and Transplantation Network/United Network for Organ Sharing data, all black/African-American kidney recipients were stratified according to transplant year into an early (1988–99) and recent era (2000–11). Patient and allograft survival among SCD recipients and those with other diagnoses were compared (early era: SCD n = 67, others n = 20,694; recent era: SCD n = 106, others n = 34,428). A secondary-matched cohort analysis compared patient and allograft survival between SCD recipients matched to recipients with other diagnoses based on recipient and donor age, gender and donor type (deceased versus living).

Results. Patient survival at 6 years was lower among SCD recipients in the early era compared with other diagnoses (55.7 versus 78.0%; P < 0.001). Six-year patient survival among sickle cell recipients improved in the recent era (69.8%; P versus early era = 0.04), although still trended toward lower survival compared with other diagnoses (80.0%; P = 0.07). Multivariate Cox proportional hazard models revealed an increased mortality risk with SCD in both eras [early: hazard ratio (HR) = 3.12; 95% confidence interval (CI): 2.15–4.54; recent: HR: 2.03; 95% CI: 1.31–3.16]. Patient survival among matched SCD recipients in the recent era was comparable to diabetic recipients (SCD: 73.1%, diabetes: 74.1%; P = 0.44).

Conclusions. Patient survival has improved among contemporary sickle cell recipients compared with an earlier cohort and is comparable to a matched cohort of diabetic kidney recipients. Appropriately selected SCD patients may receive kidney transplants with reasonable survival outcome.

INTRODUCTION

Sickle cell disease (SCD) is an inherited hemoglobinopathy arising from the substitution of valine for glutamine at the sixth amino acid of the β-globin chain. The mutation results in a poorly soluble hemoglobin tetramer when deoxygenated [1]. SCD is characterized by vaso-occlusive crises and hemolysis and kidney disease may develop from the occlusion of the vasa recta capillaries. Renal manifestations include papillary necrosis, renal infarction, painless hematuria, nephrogenic diabetes insipidus and focal segmental glomerulosclerosis [2].

Sickle cell nephropathy carries a poor survival prognosis when associated with end-stage renal disease (ESRD). In a report from the US Renal Data Systems, SCD patients with ESRD were associated with a 52% increased risk of death compared with those with other diagnoses and survival among SCD patients was lower than that of diabetic ESRD patients [3]. Sickle cell kidney transplant recipients are at a
considerably higher risk for post-transplant mortality than other black recipients without SCD, although evidence for this is derived from older cohorts of kidney recipients transplanted prior to 2000 [4, 5]. Given the improvement in patient survival following kidney transplantation in recent years [6, 7], we hypothesized that a similar increase in post-transplant survival would be observed among a more contemporary cohort of sickle cell recipients compared with those from an older era. In order to test this hypothesis, we used data from the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) to report outcomes associated with kidney transplantation among recipients with SCD.

**PATIENTS AND METHODS**

Using OPTN/UNOS data as of 3 June 2011, all primary adult kidney transplant recipients assigned a racial identity of ‘black or African-American’ were identified and stratified into two groups by the reported cause of ESRD: SCD and all other diagnoses. The study population was further subdivided into an early era, defined as a transplant year between 1988 and 1999, and a recent era, incorporating a transplant year between 2000 and 2011.

Baseline recipient and donor characteristics were described, using data from transplant candidate and recipient registration forms, as frequencies and medians (with 25th and 75th percentiles), as appropriate. Between-group comparisons were made using the chi-square test for categorical variables and the Kruskal–Wallis test for continuous variables.

The Kaplan–Meier product limit method was used to generate patient, kidney graft and death-censored graft survival curves, using the log-rank test for statistical comparison. Follow-up records were used to ascertain vital and kidney allograft status. Kidney graft survival was determined from the date of transplantation to the date of death, re-transplantation or return to dialysis. All patients were censored at the end of the study period. Cox proportional hazard models were used to calculate hazard ratios (HR) and 95% confidence intervals (95% CI) of death, kidney graft failure and death-censored graft survival, using the log-rank test for statistical comparison.

Covariates included in the model were the cause of ESRD (sickle cell versus others), recipient age (categorized as ≤25, 26–40 and >40), gender, body mass index (BMI: <18, 18–24.9 and ≥25), PRA (<20 versus ≥20%), donor type (deceased versus living) and donor age (≤35, 36–49 and ≥50).

A matched cohort study was then performed as a secondary method of controlling for differences in baseline characteristics. The matching algorithm consisted of finding all exact matches on the covariates of recipient and donor age, recipient gender and donor type (deceased versus living) from the ‘control’ group (recipients with other diagnoses) for members of the ‘treated’ group (SCD recipients). Unadjusted patient survival was calculated using the Kaplan–Meier product limit method and the stratified log-rank test was used for statistical comparison of survival curves. Hazard ratios for mortality were assessed using stratified Cox proportional hazard models.

All reported P-values were two-tailed and P of <0.05 was considered significant. Analyses were conducted using STATA Statistical Software, version 11 (StataCorp LP, College Station, TX).

**RESULTS**

**Baseline characteristics**

Table 1 describes the baseline characteristics of the study population. There were 55 122 black/African-American recipients from 1988 to 2011. In the early era (1988–99), there were 20 694 recipients, of whom 67 were assigned a diagnosis of ESRD due to SCD. In the recent era (2000–11), there were 34 428 recipients overall, of whom 106 had SCD.

SCD recipients were younger and had a lower BMI than those assigned other diagnoses. Although there was no difference in the degree of allosensitization between SCD recipients and others in the early era, a greater proportion of SCD recipients were allosensitized (panel reactive antibodies, PRA >20%) in the recent era.

Most of the transplanted kidneys originated from deceased donors in all groups. Only a small proportion of SCD recipients received an expanded criteria donor (ECD) kidney (early: 3.4%; recent: 9.9%).

The majority of recipients did not receive antibody induction in the early era, whereas over two-thirds of recipients received antibody induction in the recent era. There were no differences between SCD recipients and those with other diagnoses in the use or type of antibody induction agents in either era. Similarly, maintenance immunosuppression did not differ between SCD recipients and those with other diagnoses in either era, although there was a trend toward lower corticosteroid usage among recipients with other diagnoses in the recent era.

**Patient survival**

Figure 1a compares unadjusted patient survival in the early era between SCD recipients and those with other diagnoses. At 6 years, patient survival was lower among SCD recipients compared with recipients with other diagnoses (55.7 versus 78.0%; log-rank P <0.001). Figure 1b shows that the survival gap between SCD recipients and those with other diagnoses has diminished in the recent era. There was a 10% difference in patient survival between SCD recipients and those with other diagnoses in the recent era that was not statistically significant (at 6 years, other diagnoses: 80.0 versus sickle cell: 69.8%; log-rank P: 0.07). When comparing patient survival between SCD recipients in the early and recent era, a greater proportion of SCD recipients were alive 6 years after transplant in the recent era compared with the early era (Figure 1c: 69.8 versus 55.7%; log-rank P: 0.04).

There were no differences in the causes of death reported among SCD recipients and those with other diagnoses in either era. The most common cause of death reported in both eras was unknown (early: SCD 35.7 versus others 37.7%,
Among known causes, cardiovascular death was the most common (early: SCD 25.0 versus others 23.0%, \( P = 0.81 \); recent: SCD 20.0 versus others 21.6%, \( P = 0.86 \)) followed by infectious causes (early: SCD 21.4 versus others 12.9%, \( P = 0.18 \); recent: SCD 15.0 versus others: 15.2%, \( P = 0.98 \)).

Table 2 describes the hazard ratios for recipient death in the early and recent eras. In the early era, recipients with...
SCD had a 2.42 times increased risk of death compared with those with other diagnoses on univariate analysis (95% CI: 1.67–3.51). After adjusting for confounding factors, SCD recipients had a 3.12 times increased risk of death compared with those with other diagnoses (95% CI: 2.15–4.54). In the recent era, there was no association between the cause of ESRD (SCD versus others) and death on univariate analysis, but after multivariate analysis, SCD recipients were associated with a 2.03 times increased risk of death compared with other diagnoses (95% CI: 1.31–3.16).

**Graft survival**

Figure 2a compares unadjusted kidney graft survival between SCD recipients and recipients with other diagnoses in the early and recent eras. In the early era, there was no difference in kidney graft survival over 6 years (SCD: 45.9 versus others: 50.7%; log-rank P: 0.24). In the recent era, kidney graft survival was lower among SCD recipients compared with those with other diagnoses (50.8 versus 60.0%; log-rank P: 0.04). There was no difference in kidney graft survival between SCD recipients in the early and recent eras (log-rank P: 0.34).

Figure 2b compares the unadjusted death-censored kidney graft survival between SCD recipients and those with other diagnoses. There was no difference in death-censored kidney graft survival over 6 years between either group in both the early (SCD 67.3 versus others 60.7%; log-rank P = 0.48) and recent eras (SCD 65.0 versus others 70.8%; log-rank P: 0.07).

Table 2 shows the hazard ratios for kidney graft and death-censored kidney graft failure in the early and recent eras. On univariate analysis, SCD recipients were not at increased risk for kidney graft failure compared with recipients with other diagnoses in the early era (HR: 1.22; 95% CI: 0.87–1.70). After adjusting for confounding factors, there was no association between SCD and graft failure (HR: 1.18; 95% CI: 0.85–1.65). In the recent era, SCD recipients were at increased risk for graft failure compared with recipients with other diagnoses on univariate analysis (HR: 1.38; 95% CI: 1.01–1.89). There was a trend toward increased risk of kidney graft failure among SCD recipients compared with those with other diagnoses after adjusting for confounding factors (HR: 1.33; 95% CI: 0.97–1.82). On multivariate analysis, SCD was not associated with an increased risk of death-censored kidney graft loss compared with other diagnoses in both the early (HR: 0.74; 95% CI: 0.46–1.17) and recent eras (HR: 1.18; 95% CI: 0.81–1.72).

**Matched cohort analysis**

A matched cohort subgroup analysis was conducted in order to account for differences in baseline characteristics between SCD recipients and recipients with other diagnoses. After exact matching on the characteristics of age, gender, donor type (living versus deceased) and donor age, a total of 53 SCD recipients in the early era were matched to 183 recipients with other diagnoses. There were 14 SCD recipients who did not have an exact match on the above variables in the early era and were excluded from the matched cohort analysis. In the recent era, 86 SCD recipients were matched to 341 recipients with other diagnoses; 20 SCD recipients did not have an exact match on the above variables and were excluded from the analysis.

Figure 3 compares patient survival between matched SCD recipients and recipients with other diagnoses in the early and recent eras. In the early era, SCD recipients had lower survival over 6 years compared with those with other diagnoses (55.7 versus 83.4%; stratified log-rank P < 0.001) and was associated with a 3.56 times increased risk of death compared with matched recipients with other diagnoses (95% CI: 1.79–7.09). In the recent era, SCD recipients also had lower survival compared with recipients with other diagnoses (71.0 versus 84.1%; stratified log-rank P = 0.001) and was associated with a 3.42 times increased risk of death compared with matched recipients with other diagnoses (95% CI: 1.78–6.62).
Table 2. Cox proportional hazard models for patient death, kidney graft loss and death-censored kidney graft loss in the early era (1988–99) and recent era (2000–11)

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<td>Sickle cell versus others</td>
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<td>Sickle cell versus others</td>
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<td>Death-censored kidney graft failure</td>
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<td>Recent era</td>
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<td>Death-censored kidney graft failure</td>
<td>1.42 (0.97–2.07)</td>
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Covariates included in the model include recipient age, recipient gender, BMI, PRA, donor type (deceased versus living) and donor age.

**FIGURE 2:** Comparison of (a) kidney graft survival and (b) death-censored kidney graft survival between sickle cell recipients and those with other diagnoses in the early (1988–99) and recent eras (2000–11).
risk of death compared with matched recipients with other diagnoses (95% CI: 1.58 – 7.43).

Comparison of patient survival among sickle cell recipients to specific ESRD causes in the recent era

In order to better characterize the survival after kidney transplantation among SCD in the recent era, we compared the survival among SCD recipients with that of recipients with diabetes, hypertension and glomerulonephritis as a reported cause of ESRD. For this subgroup analysis, SCD recipients in the recent era were exact matched with other recipients on the covariates of age, gender, donor type (deceased versus living) and donor age category (categorized as ≤35, 36–49 and ≥50).

Diabetes

A total of 91 SCD recipients were exact matched with 610 diabetic recipients on these covariates. Exact matching was performed on donor age category instead of donor age to allow the selection of an adequate number of matched recipients. Nevertheless, there was no significant difference in the donor age between SCD and matched diabetic recipients (mean age: SCD 36.3 ± 15.7; others 36.1 ± 15.6; standardized difference: 0.007).

There was no difference in the survival over 6 years among matched SCD and diabetic recipients (SCD: 73.1% versus diabetes: 74.1%; stratified log-rank P = 0.44). A stratified Cox regression model revealed that SCD recipients were not at increased risk of death compared with matched diabetic recipients (HR: 1.25; 95% CI: 0.70 – 2.22).

Hypertension

There were 102 SCD recipients who were exact matched on the above covariates to 905 recipients with hypertension as a cause of ESRD. There was no difference in the donor age between SCD and matched hypertensive recipients (mean age: SCD 36.2 ± 15.6; hypertension 36.2 ± 14.6; standardized difference: 0.06).

SCD recipients had decreased survival over 6 years compared with matched hypertensive kidney recipients (SCD: 68.8 versus others: 86.9%; stratified log-rank P < 0.001). A stratified Cox regression model revealed that SCD recipients were associated with a 2.86 times greater risk of death compared with matched hypertensive recipients (95% CI: 1.61 – 5.06).

Glomerulonephritis

A total of 104 SCD recipients were matched with 924 recipients with glomerulonephritis as a cause of ESRD. There was no significant difference in the donor age between SCD recipients and recipients with glomerulonephritis (mean age: SCD 36.2 ± 15.6; glomerulonephritis 36.2 ± 14.4; standardized difference: 0.06). SCD recipients had lower survival compared with recipients with glomerulonephritis over 6 years (70.6 versus 89.3%; stratified log-rank P < 0.001). SCD recipients were at a 2.80 times increased risk of death compared with recipients with glomerulonephritis (95% CI: 1.59 – 4.93).

DISCUSSION

Few patients with SCD have received kidney transplants in the USA, representing only 0.003% of the overall black/African-American kidney transplant population from 1988 to 2011. In a historical cohort of black/African-American kidney transplant recipients in the USA from 1988 to 1999, SCD recipients had markedly lower survival compared with those with other causes of ESRD. Our study shows that the patient survival among SCD kidney recipients has improved in more recent years from 2000 to 2011. There was a trend toward a lower unadjusted patient survival among SCD
recipients in the recent era compared with those with all other diagnoses combined and the patient survival was comparable to a matched cohort of diabetic recipients.

There is a low prevalence of end-stage sickle cell nephropathy in the USA, representing only 0.1% of incident ESRD patients [3]; those with sickle cell nephropathy are less likely to be placed on the kidney transplant waiting list and to receive kidney transplants in comparison with age and race-matched controls [3]. Our study also affirms that kidney transplantation is uncommonly performed among candidates with end-stage sickle cell nephropathy. This finding may potentially reflect the systemic nature of the disease and poor health status of many SCD patients. SCD is associated with thrombotic events, pulmonary hypertension, infections, cardiac disease and cirrhosis, all of which may deter referral for transplantation [8, 9].

The findings from the earlier cohort in our study are supported by those observed in previous reports. Ojo et al. [4] reported that SCD recipients from 1984 to 1996 had a survival of 59% at 3 years compared with 81% among black recipients with other diagnoses. In our study, 71% of SCD recipients remained alive at 3 years, a figure which is higher than that reported by Ojo et al. These discrepant results are likely explained by a difference in the study period between the two studies. In a report from Bleyer et al. incorporating kidney recipients reported to the UNOS registry from a similar time period (1987–96) as the historical cohort in our study (1988–99), patient survival at 3 years among the SCD kidney recipients was 75.0% and SCD recipients were associated with a 7.9 times higher risk of post-transplant death compared with the reference condition of IgA nephropathy (95% CI: 4.3–14.5) [5]. However, IgA nephropathy may not be the appropriate reference condition when comparing to SCD. It has been reported that IgA nephropathy is uncommon amongst African-Americans [10, 11], and therefore a comparison of post-transplant survival between SCD and IgA nephropathy recipients may not adequately control for the effect of race on outcome. In comparison with the Bleyer study, SCD recipients in our study had a smaller, albeit considerably increased risk of death, compared with black recipients with other diagnoses in the earlier era (HR: 3.12; 95% CI: 2.15–4.54).

In the recent era, SCD recipients had higher post-transplant patient survival than the early era, whereas the survival did not appreciably change among black recipients with other diagnoses. SCD recipients remained at increased risk for death in the recent era after multivariate adjustment compared with recipients with other diagnoses (HR: 2.03; 95% CI: 1.31–3.16). When controlling for confounding factors by exact matching on recipient and donor characteristics, SCD recipients had a lower patient survival than matched recipients with hypertension and glomerulonephritis as a cause of ESRD, but comparable survival to that of diabetic ESRD recipients (73.1 versus diabetes: 74.1%; P = 0.44).

We examined whether SCD kidney transplant recipients were at increased risk of allograft failure, given the prevalence of kidney disorders in patients with SCD. It has been reported that 68% of SCD patients have albuminuria and 21% have some degree of renal insufficiency [12]. Focal and segmental glomerulosclerosis is the hallmark glomerular lesion associated with SCD, but thrombotic microangiopathy and membranoproliferative glomerulonephritis have also been described [13, 14]. Other renal manifestations of SCD include asymptomatic hematuria, papillary necrosis, renal infarction, renal hemosiderosis and renal medullary carcinoma [14–17].

In our study, there was no difference in kidney graft survival observed in SCD recipients between the early and recent eras (early: 45.9%; late: 50.7%; log-rank P = 0.34). Although the lack of statistical difference may be related to inadequate statistical power (a power calculation to detect a statistically significant difference of 4.8% with the current sample size was only 0.09), the observed difference in graft survival at 6 years among SCD recipients in the early and recent eras was small and not clinically significant. On the other hand, SCD recipients were observed to have a lower unadjusted graft survival compared with recipients with other diagnoses in the recent era (SCD: 50.8 versus others: 60.0%; log-rank P: 0.04). These observations suggest that close monitoring for early signs of graft dysfunction among SCD recipients may be warranted.

Our study was limited by factors that are inherent to registry analysis. Given the lack of information on SCD-related co-morbidities, we were unable to account for the severity of the SCD. Furthermore, we had no information on the degree of anemia or frequency of vaso-occlusive crises. Because of these issues, we were unable to discern what factors are responsible for the increased survival observed in the recent era. There were no differences in either era in the causes of death among SCD recipients and those with other diagnoses. Because of a limited number of events, we cannot conclude whether a significant change in the distribution of causes of death has developed in recent years. We presume that improved survival observed in the SCD kidney transplant population reflects better selection of candidates for transplantation in more recent years. Nevertheless, we cannot exclude the possibility that the improved survival seen among SCD kidney recipients is due to advances in the care of the patient with SCD. Indeed, the introduction of hydroxyurea therapy was shown to reduce the frequency of acute chest syndrome, need for transfusions and number of hospitalizations [18]. In 2003, long-term follow-up of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia trial established that the use of hydroxyurea in SCD patients was associated with a 40% reduction in mortality [19]. Although the overall experience of kidney transplant recipients with SCD is limited, our data show a relatively substantial increase in patient survival over 6 years and suggests that kidney transplantation is a reasonable consideration for appropriately selected SCD candidates in the current era.

In conclusion, this study has shown that patient survival among kidney transplant recipients with SCD has improved in the recent era and 6-year survival is comparable to that of black recipients with diabetes as a cause of ESRD. SCD recipients may be at higher risk of kidney allograft failure, but this association was not seen after adjusting for patient death. These observations are of utility when considering potential sickle cell candidates for kidney transplant.
Data reported here have been taken from the Organ Procurement Transplant Network/United Network for Organ Sharing (OPTN/UNOS) database as of 31 March 2011. This work was supported in part by Health Resources and Services Administration contract 231-00-0115. The content is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products or organizations imply endorsement by the US Government.

The results presented in this paper have not been published previously in whole or part, except in abstract format. There is no conflict of interest to declare.


Received for publication: 26.9.2012; Accepted in revised form: 20.11.2012