REGULAR ARTICLE

blood advances

Long-term survival with sickle cell disease: a nationwide cohort study of Medicare and Medicaid beneficiaries

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Key Points

- The life expectancy among Medicare and Medicaid beneficiaries with sickle cell disease was 52.6 years.
- Individuals insured by Medicare for disabilities or end-stage renal disease and dually insured by Medicare and Medicaid had worse survival.

To our knowledge, we report the first population-based period life table, the expected lifetime survival for Medicare and Medicaid beneficiaries with sickle cell disease (SCD), and the disparities in survival by insurance types in the United States. We constructed a retrospective cohort of individuals with diagnosed SCD receiving common care (any real-world patterns of care except transplant) based on nationwide Medicare and Medicaid claim data (2008-2016), covering beneficiaries in all 50 states. We analyzed lifetime survival probabilities using Kaplan-Meier curves and projected life expectancies at various ages for all, stratified by sex and insurance types. Our analysis included 94 616 individuals with SCD that have not undergone any transplant. Life expectancy at birth was 52.6 years (95% confidence interval: 51.9-53.4). Compared with the adults covered by Medicaid only, those covered by Medicare for disabilities or end-stage renal disease and those dually insured by Medicare and Medicaid had significantly worse life expectancy. Similarly, for beneficiaries aged ≥65 years, these 2 insurance types were associated with significantly shorter life expectancy than those enrolled in Medicare old age and survivor's insurance. Our study underscores the persistent life expectancy shortfall for patients with SCD, the burden of premature mortality during adulthood, and survival disparities by insurance status.

Introduction

Sickle cell disease (SCD) is a group of genetically inherited disorders of hemoglobin that affects ~100 000 people in the United States.[1] The prevalence of SCD is disproportionately higher among people of African descent than other ethnicities.[1] An individual with SCD is prone to a wide range of acute and chronic life-threatening complications, such as acute pain crisis, stroke, acute chest syndrome, chronic pain, symptomatic anemia, and an increased risk of infections and organ damage.[1,2]

Owing to the widespread adoption of several medical interventions over the past few decades, including hydroxyurea, newborn screening, pneumococcal vaccination, and prophylactic antibiotics, the survival rate of children with SCD in the United States has considerably improved.[3-5] However, the complications of SCD can still lead to premature mortality during adulthood, and thereby the life expectancy of individuals with SCD remains well below the general population average.[3-5] According to a recent study, the life expectancy for a US birth cohort with SCD is ~2 decades shorter than that of

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The full-text version of this article contains a data supplement.

those without SCD.[6] However, these projections were made based on a simulation model informed via summary statistics rather than an empirical estimation from individual data. No population-level individual data–based periodic life table exists for individuals with SCD.

Most people living with SCD in the United States are covered by public insurance, with Medicaid as the major source of coverage.[7,8] Insurance coverage plays a vital role in patients' access to necessary and appropriate health care management, thus affecting their mortality outcomes.[8-10] Prior studies examined the mortality of Medicaid or Medicaid beneficiaries with SCD.[11-14] Yet, these studies were limited to a few states[11] or hospital settings,[14] focused on a single public insurance type,[11-13] or did not report age-specific information.[11,13,14]

Moreover, the survival of individuals with SCD may differ across the types of public insurance. For example, some Medicare beneficiaries are also enrolled in Medicaid. Those dual-eligible individuals tend to experience a higher burden of chronic diseases and poorer survival outcomes than single eligibles.[15] In addition, evidence has shown that younger people entitled to Medicare because of disabilities or end-stage renal diseases (ESRD) face an increased mortality risk.[16,17] Although the disparity in survival by public insurance type has been explored in the general population, little is known about the SCD population.

To address the identified gaps in knowledge, we aimed to estimate period life tables among Medicare and Medicaid beneficiaries with SCD and examine the potential disparities in survival by insurance type based on US nationwide claims data.

Methods

Data source

Data for this study were obtained from the Medicaid Analytic eXtract files and Medicare Part A and B Fee-for-Service claims covering enrollees from 2008 to 2016. The data contain demographic information, insurance enrollment status, and administrative claims for 100% of the individuals with SCD covered by Medicaid or Medicare in all 50 states. In addition, information on the exact date of death was derived from death certificates provided through the linkage with the National Death Index. The details about the data files can be found on the website of the Centers for Medicare and Medicaid Services Research Data Assistance Center.[18] This study was approved by the University of Washington Institutional Review Board.

Study population

We conducted a retrospective cohort study of Medicare and Medicaid beneficiaries with SCD in the United States. They were identified based on the SCD indicator developed by the Centers for Medicare & Medicaid Services Chronic Conditions Data Warehouse (CCW). The CCW's algorithm requires 3 or more nondrug claims of any service type with diagnosis codes for SCD (supplemental Table 1) during a 5-year "look-back" period.[19] We included individuals who were continuously enrolled for 12 months after the entry date.[20] Further, we restricted the follow-up of our cohort to those receiving "common care," consisting of all-comers who either are receiving no treatment or hydroxyurea or transfusions (but did not receive hematopoietic stem cell transplant).[20]

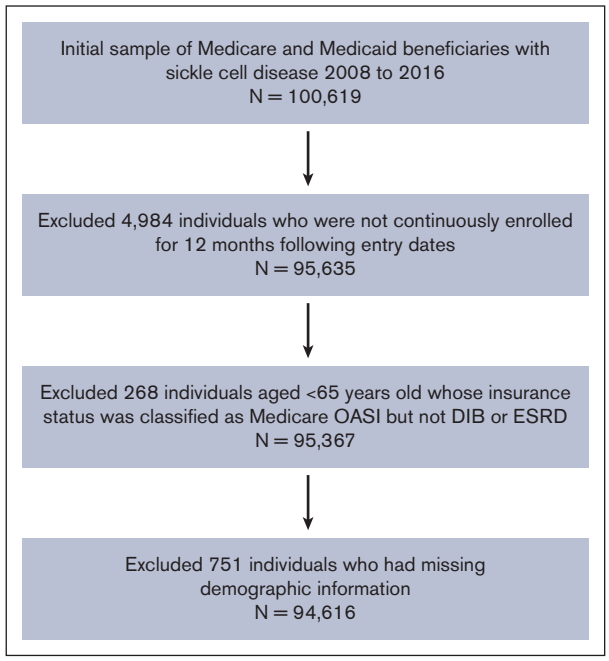

Figure 1. Patient selection flowchart.

This common care cohort was identified to serve as a control group for individuals who would be eligible for novel disease-modifying or gene therapies in SCD.[20] The insurance statuses for individuals in our common care cohort were classified as Medicare old age and survivor's insurance (OASI) only, Medicare disability insurance benefits (DIB) or ESRD only, Medicaid only, and dual-eligible individuals (defined as those who are enrolled in both Medicare and Medicaid at least some time during their lives). We excluded the individuals aged <65 years whose insurance status was classified as Medicare OASI but not DIB or ESRD (Figure 1). The Centers for Medicare and Medicaid Services obtained information about the original reason for Medicare entitlement (OASI, DIB, or ESRD) from the Social Security Administration and Railroad Retirement Board record systems.[18] Individuals were followed until death, the end of enrollment, or receiving hematopoietic stem cell transplantation, whichever occurred first. Only the longest enrollment period was included in the analysis for those with multiple distinct enrollment periods during the study period.

Study variables

The outcome variable was time to event, from the age of enrollment to death. The end of enrollment or receiving hematopoietic stem cell transplantation were considered censoring events. We also summarized the following demographic characteristics by insurance status: age at entry and exit, sex, region (Northeast, Midwest, South, and West), race (White, Black, Hispanic, and others), and birth cohort (classified according to the year of birth: 1900-1939, 1940-1959, 1960-1979, 1980-1999, 2000-2004, 2005-2009, and 2010-2016, based on population size as the number of individuals with SCD decreases rapidly with age). The demographic characteristics were ascertained at the index date, when the first use with a diagnosis of SCD occurred.

Table 1. Descriptive characteristics for individuals with SCD by insurance status

	Total (N = 94 616)	Medicare OASI (N= 4 475)	Medicare DIB or ESRD (N = 4 153)	Medicaid (N = 45 068)	Dual eligibles (N = 40 920)
Mean age at entry (y)	26.6 (22.6)	73.4 (7.5)	50.2 (13.5)	15.4 (14.9)	31.4 (21.2)
Mean age at exit (y)	33.0 (22.6)	79.9 (7.9)	56.7 (13.9)	21.4 (14.7)	38.1 (21.3)
Claims	7 331 038	357 086	330 363	3 331 488	3 312 101
Sex					
Male	40 877 (43%)	1 737 (39%)	1 857 (45%)	20 452 (45%)	16 831 (41%)
Female	53 739 (57%)	2 738 (61%)	2 296 (55%)	24 616 (55%)	24 089 (59%)
Race					
White	6 476 (7%)	2 389 (53%)	478 (12%)	1 319 (3%)	2 290 (6%)
Black	70 064 (74%)	1 869 (42%)	3 486 (84%)	31 651 (70%)	33 058 (81%)
Hispanic	4 069 (4%)	97 (2%)	84 (2%)	2 189 (5%)	1 699 (4%)
Other	14 007 (15%)	120 (3%)	105 (3%)	9 909 (22%)	3 873 (10%)
Region					
Northeast	18 630 (20%)	951 (21%)	694 (17%)	10 054 (22%)	6 931 (17%)
Midwest	17 460 (19%)	798 (18%)	627 (15%)	7 428 (17%)	8 607 (21%)
South	50 428 (53%)	2 150 (48%)	2 526 (61%)	23 592 (52%)	22 160 (54%)
West	8 098 (9%)	576 (13%)	306 (7%)	3 994 (9%)	3 222 (8%)
Birth cohort					
1900-1939	6 140 (7%)	3 107 (69%)	317 (8%)	38 (0%)	2 678 (7%)
1940-1959	11 317 (12%)	1 368 (31%)	2 057 (50%)	1 837 (4%)	6 055 (15%)
1960-1979	19 306 (20%)	0 (0%)	1 443 (35%)	6 355 (14%)	11 508 (28%)
1980-1999	33 478 (35%)	0 (0%)	336 (8%)	18 720 (42%)	14 422 (35%)
2000-2004	8 281 (9%)	0 (0%)	0 (0%)	6 289 (14%)	1 992 (5%)
2005-2009	9 959 (11%)	0 (0%)	0 (0%)	7 433 (17%)	2 526 (6%)
2010-2016	6 135 (7%)	0 (0%)	0 (0%)	4 396 (10%)	1 739 (4%)

Analysis

We used the Kaplan-Meier approach to estimate period life tables and lifetime survival curves for individuals with SCD. Using these period life tables, we computed expected life expectancies at birth and ages 18, 35, 45, 65, and 85 years old. The analysis was further stratified by sex and insurance status. The risk set accounted for delayed entry (left truncation) and right censoring of individuals enrolled in the insurance program. Clustered bootstrapped replicates (1000 deviates) were used to generate 95% confidence intervals (CIs) for the survival probabilities and life expectancies.

Furthermore, we estimated the life expectancies for the Black and non-Black groups separately to identify the potential racial disparity. Finally, because there might be a disparity between individuals with Medicare DIB and those with Medicare ESRD, additional analyses were performed with Medicare DIB or ESRD being further classified as Medicare DIB only and Medicare ESRD only.

The Kaplan-Meier curves were generated using the package ggplot2 in Rstudio 2022.02.0, and the data manipulation was performed in Stata/MP 17.0.

Results

We included 94 616 individuals with SCD between 2008 and 2016, of whom 5% had Medicare OASI, 4% had Medicare DIB or ESRD, 48% had Medicaid, and 43% were dually eligible for Medicare and Medicaid (Table 1). The mean entry ages were 73.4 (standard deviation [SD]: 7.5), 50.2 (SD: 13.5), 15.4 (SD: 14.9), and 31.4 (SD: 21.2) years for Medicare OASI, Medicare DIB or ESRD, Medicaid, and dual-eligible cohorts, respectively. The mean entry age overall was 26.6 years (SD: 22.5) across all the insurance types. The mean and median follow-up times were 6 (SD: 3) and 7 (interquartile range: 4-9) years, respectively. Most of the included individuals were Black (74%) and most resided in the South (53%) at the index date. Similar racial and regional distribution was found across the insurance types, except that 53% of the Medicare OASI beneficiaries were White.

The Kaplan-Meier curve in Figure 2 depicts the survival probabilities over age for all the included individuals. They maintained high survival with a steady decline during childhood; the survival probability at 18 years old was 0.980 (95% CI: 0.977-0.984). After transitioning into adulthood, however, their survival declined rapidly. The survival probabilities were 0.804 (95% CI: 0.795-0.815), 0.628 (95% CI: 0.616-0.641), 0.267 (95% CI: 0.255-0.279), and 0.070 (95% CI: 0.064-0.075) at 30, 45, 65, and 85 years old, respectively. Females had significantly greater survival likelihoods than males during adulthood.

Figure 3 presents the Kaplan-Meier curve for each insurance type. The Medicaid and dual-eligible cohorts had a similar probability of survival till 18 years of age, with 0.979 (95% CI: 0.975-0.983) for the former and 0.984 (0.978-0.989) for the latter. The probability of

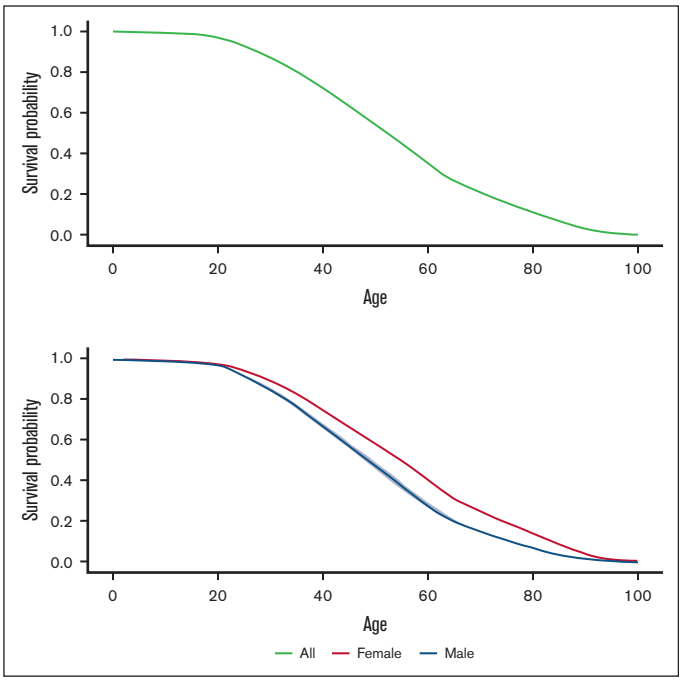

Figure 2. Survival curves for all the individuals with SCD (top panel) and by sex (bottom panel).

survival to 45 years old was highest among individuals with Medicaid across the insurance types, estimated to be 0.707 (95% CI: 0.688-0.728). At the age of 85 years, the survival probability was 0.343 (95% CI: 0.318-0.371) for the elderly cohort covered by Medicare OASI, which was better than the other cohorts. The survival curve for each insurance cohort by sex can be found in Figure 4. The females who were covered by Medicaid or were dually eligible experienced greater survival probabilities than the males for most of their lifetime. The supplementary curves showing the cumulative mortality over age can be found in supplemental Appendices 1-3.

The life expectancy of all the Medicare and Medicaid beneficiaries with SCD was 52.6 years (95% CI: 51.9-53.4) at birth, 35.4 years (95% CI: 34.9-36.1) at 18 years old, 24.1 years (95% CI: 23.7-24.6) at 35 years old, 19.6 years (95% CI: 19.2-20.0) at 45 years old, 13.2 years (95% CI: 13.0-13.5) at 65 years old, and 5.4 years (95% CI: 5.1-5.7) at 85 years old (Table 2). Similar to the difference by sex in survival probability observed above, the life expectancy at birth for females (55.0 [95% CI: 54.1-56.1]) was significantly longer compared with that of males (49.3 [95% CI: 48.2-50.4]). The Medicaid cohort had a life expectancy of 39.8 years (95% CI: 35.9-44.9) at 18 years old, better than the Medicare DIB or ESRD and dual-eligible cohorts. At 65 years old, the life expectancy for individuals with Medicare OASI (15.2 [95% CI: 14.5-16.1]) was significantly longer than for those with Medicare DIB or ESRD and dual-eligible patients.

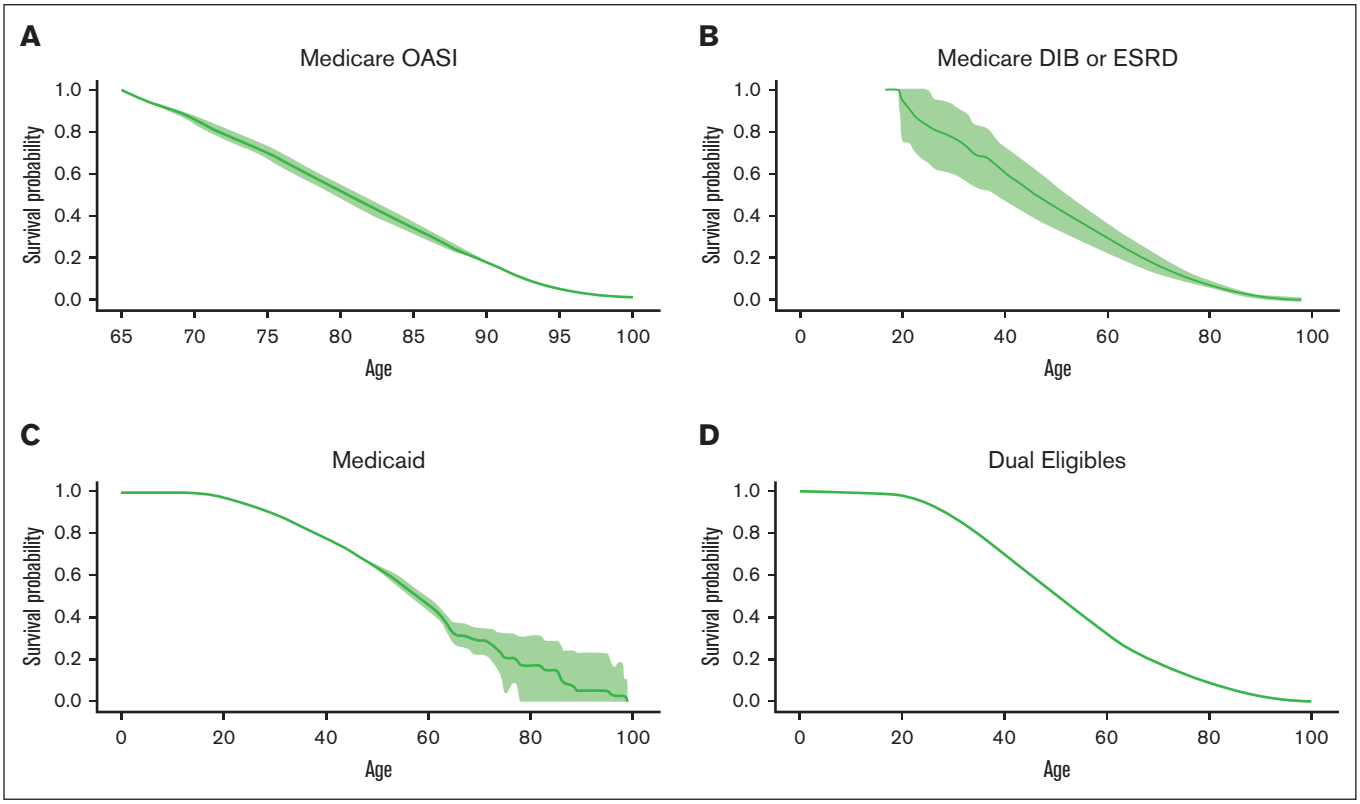

Figure 3. Survival curves for individuals with SCD by insurance status. Medicare OASI (A), Medicare DIB or ESRD (B), Medicaid (C), and dually eligible for Medicare and Medicaid (D).

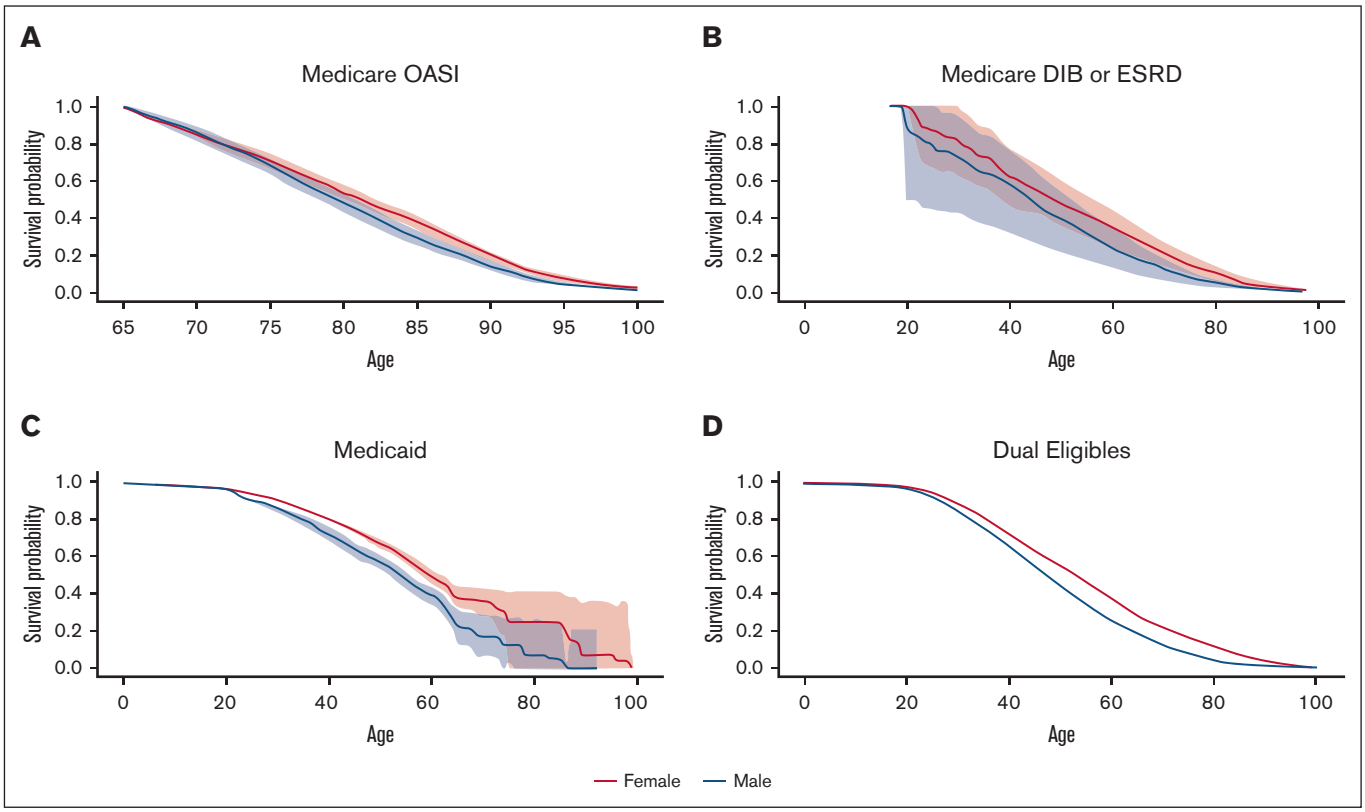

Figure 4. Survival curves for individuals with SCD by insurance status and sex. Medicare OASI (A), Medicare DIB or ESRD (B), Medicaid (C), and dually eligible for Medicare and Medicaid (D).

The results of the additional analyses can be found in supplemental Tables 2 and 3. Black individuals had a significantly shorter life expectancy at birth (52.2 [95% CI: 51.4-53.1]) than non-Black individuals (55.1 [95% CI: 53.2-57.0]). In the second analysis, the survival was significantly worse for adults with Medicare ESRD and those with both Medicare DIB and ESRD compared with those with Medicare DIB.

Discussion

Using a Medicare and Medicaid administrative database linked to the National Death Index, we estimated the survival of individuals with SCD and projected their life expectancies at various ages. We found that this population's life expectancy at birth was 52.6 years, with females presenting superior survival to males. Furthermore, adults aged 18 to 64 years enrolled in Medicare DIB or ESRD or dually eligible for Medicare and Medicaid had a higher death rate than those covered by Medicaid. Similarly, for enrollees aged ≥65 years, these 2 insurance types were associated with significantly worse survival relative to Medicare OASI.

Previous studies reported the mortality of individuals with SCD in the United States.[6,11-14] However, these analyses were conducted based on aggregated statistics or limited individual-level data. To the best of our knowledge, this is the first United States nationwide investigation into lifetime survival for individuals with SCD covered by Medicare and Medicaid and disparities in survival by public insurance type, using comprehensive claims data collected from all 50 states.

A recent study simulated the life trajectory and mortality outcomes of a United States SCD birth cohort based on data from the US Centers for Disease Control and Prevention, the National Newborn Screening Information System, and published mortality literature.[6] Consistent with our estimate, they projected a life expectancy of 54 years at birth. One discrepancy is that their projections did not differ between males and females with SCD. We could not explain this discrepancy because their article did not provide details about the sex-specific mortality inputs used. However, the published mortality study they relied on[21] and other prior studies[22,23] did estimate a higher mean age of death in females than males with SCD.

Based on the 2016 US Centers for Disease Control and Prevention life table, the life expectancy of the general Black population was 75 years.[24] Similarly, Lubeck et al[6] estimated a life expectancy of 76 years for a non-SCD population matched on age, sex, and race or ethnicity with the SCD population. Both are substantially longer than our estimate for the Medicare and Medicaid beneficiaries with SCD. Evidently, the life expectancy gap persists among patients with SCD, even though they are protected by public insurance. Furthermore, the survival rates of individuals with SCD remained high during childhood but declined significantly after adulthood, echoing the general recognition that survivorship into adulthood for children with SCD is now a less problematic issue but early mortality among adults remains concerning.[3] Our study also suggests that Black beneficiaries may experience worse survival outcomes than non-Black beneficiaries. However, the

Table 2. Life expectancies (95% CI) at different ages for individuals with SCD by insurance status

Age	All	Female	Male
Total			
Birth	52.6 (51.9-53.4)	55.0 (54.1-56.1)	49.3 (48.2-50.4)
18	35.4 (34.9-36.1)	37.8 (37.0-38.6)	32.2 (31.3-33.1)
35	24.1 (23.7-24.6)	26.0 (25.4-26.6)	21.4 (20.7-22.1)
45	19.6 (19.2-20.0)	21.3 (20.8-21.8)	17.1 (16.6-17.6)
65	13.2 (13.0-13.5)	14.0 (13.7-14.4)	11.9 (11.6-12.2)
85	5.4 (5.1-5.7)	5.6 (5.2-6.0)	4.9 (4.5-5.4)
Medicare OASI			
65	15.2 (14.5-16.1)	15.8 (14.7-16.9)	14.5 (13.2-15.7)
85	5.4 (5.0-5.8)	5.6 (5.2-6.1)	5.0 (4.4-5.5)
Medicare DIB or ESRD			
18	29.7 (23.0-35.7)	32.5 (25.0-39.5)	27.0 (15.4-35.7)
35	23.0 (22.5-23.8)	24.4 (23.4-25.5)	21.4 (20.7-22.5)
45	18.9 (18.4-19.5)	20.7 (19.9-21.6)	16.7 (15.9-17.5)
65	11.2 (10.7-11.7)	12.1 (11.0-13.2)	10.1 (9.4-11.0)
85	4.7 (3.5-6.1)	5.0 (3.4-7.0)	4.2 (2.3-6.0)
Medicaid			
Birth	56.8 (52.8-62.0)	60.0 (54.3-67.4)	51.8 (48.4-57.8)
18	39.8 (35.9-44.9)	43.0 (37.4-50.1)	34.8 (31.6-40.6)
35	28.0 (24.0-33.5)	30.7 (24.8-38.3)	23.5 (20.4-29.6)
45	22.3 (17.7-28.4)	24.7 (18.3-32.9)	18.1 (14.7-24.8)
65	16.1 (8.1-25.3)	18.2 (7.4-29.8)	11.3 (5.6-22.2)
85	4.8 (0.0-9.9)	4.6 (0.0-11.6)	0.0 (0.0-5.2)
Dual eligibles			
Birth	51.1 (50.1-52.0)	53.4 (52.1-54.7)	47.9 (46.6-49.3)
18	33.7 (33.1-34.5)	36.0 (35.1-37.0)	30.7 (29.6-31.7)
35	22.5 (22.0-23.1)	24.4 (23.8-25.1)	19.8 (19.1-20.6)
45	18.4 (17.9-18.8)	20.1 (19.6-20.7)	15.7 (15.0-16.4)
65	12.1 (11.8-12.5)	13.0 (12.6-13.5)	9.9 (9.4-10.4)
85	5.3 (4.9-5.8)	5.4 (5.0-5.9)	5.0 (4.3-5.8)

potential measurement error of race coding in claims data warrants caution in interpreting the race-specific results.

Another critical study finding is that the survival of adults with SCD varies across public insurance types. We demonstrate that ESRD, disability (an eligible criterion for Medicare regardless of age), or dual-eligible status remains a significant predictor of worse survival among adults with SCD.

Chronic kidney disease is a common complication among SCD individuals, and a fraction of them will progress to ESRD.[25] It has been shown that patients with SCD with ESRD have a remarkably inferior prognosis, associated with a mortality rate of 26% within the first year of initiating renal replacement therapy.[25] Although the premature death attributable to ESRD seems well understood, more research would be beneficial for characterizing and explaining premature death for disabled or dual-eligible adults with SCD. The existing literature has extensively explored excess deaths among disabled individuals in the general community and in other disease areas, which can be explained by clinical comorbidities, unhealthy behaviors, poor access to preventive services and high-quality health care, and low socioeconomic status,[26-28] yet there is little knowledge about the mechanism in the SCD population. Similarly, it is well recognized that the dual-eligible individuals are a vulnerable population with some of the most complex and expensive health care needs.[29] They are more likely to have fewer socioeconomic resources, more chronic conditions, and poorer survival outcomes than single eligibles.[15,30-32] Future studies should uncover factors influencing survival outcomes and explore policy options to address the unmet needs of the disabled or dually eligible population with SCD.

The major strength of our study is that, with the claims data from all 50 states, we provide the US nationwide estimates of survival among both Medicare and Medicaid beneficiaries with SCD. Moreover, leveraging this large database covering ~100 000 individuals, we created a comprehensive catalog of survival profiles at various ages for all the individuals and by sex and insurance type. Additionally, the Medicare and Medicaid claims data was linked to the National Death Index, providing accurate death data for these individuals. Finally, appropriate statistical methods were used to produce the survival estimates.

Our study is not without limitations. First, our analyses relied on Medicare and Medicare beneficiaries and thus may not be generalizable to other SCD populations such as commercially insured or uninsured individuals. Studies have shown that individuals with commercial insurance may experience life-threatening complications (eg, vaso-occlusive crisis) less frequently and have greater access to health care than those covered by Medicaid.[33,34] We also should not ignore the possibility that mortality risk may be even higher among uninsured individuals because of health care access issues.[34] Second, CCW identified the individuals with SCD using an administrative claims-based definition. Misclassifications may be inevitable, although the definition has been validated with a sensitivity of 0.96.[35] Third, although it is well recognized that the disease severity may differ based on the genotypes of SCD, we did not stratify the analysis by genotype because of the limited sample size and the accuracy of identifying these subsets in claims data. Future studies could close this knowledge gap using appropriate genotype-specific data sets. Finally, albeit the use of recently available Medicare and Medicaid data, the treatment pattern among the older individuals might not reflect the evolvements in medical interventions over the past decades, such as the use of penicillin prophylaxis and medications like hydroxyurea. Also, our analysis did not capture the possible change in health outcomes due to the uptake of recently approved emerging therapies, which have been phased in over recent years. We recommend future research to investigate the latest survival trends in the SCD population, reflecting the quickly evolving landscape of SCD treatments.

Conclusions

We provide US nationwide long-term survival estimates for Medicare and Medicaid beneficiaries with SCD. Our findings highlight the persistent life expectancy gap for patients with SCD and the enduring premature mortality throughout adulthood. This gap has improved little in recent decades. We also identify the inferior

survival among those with Medicare DIB or ESRD and those dually eligible for Medicare and Medicaid. Further research should explore the clinical and socioeconomic factors that can explain the disparity across the insurance types.

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Authorship

Contribution: A.B., S.D.R., B.D., and M.A.B. conceived of the study; B.J., K.M.J., and A.B. conducted the analyses; B.J. wrote the first draft of the manuscript; all authors critically commented on the manuscript and approved the final version; and A.B. is the guarantor of the manuscript.

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