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REVIEW ARTICLE

Risk factors associated with increased emergency department utilization in patients with sickle cell disease: a systematic literature review

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Abstract

Sickle cell disease (SCD), a genetic disorder affecting up to 100,000 patients in the USA, impacts multiple organ systems. The emergency department (ED) is frequently utilized by patients with SCD who have severe pain from vaso-occlusive crises. The goal of this systematic literature review is to identify predictors for ED use among patients with SCD in the USA, as high ED reliance is not ideal because of the potential for discontinuity of care as well as higher costs. PubMed and Embase were searched for articles containing the keywords "sickle cell disease" AND ("emergency" OR "acute care") AND ("utilization" OR "health care") published between 2000 and 26 September 2019. A total of 26 publications were identified meeting the following inclusion criteria: report of ED or acute care clinic use; report of health care utilization for SCD; and report of ED visits independent of hospital admission, ED revisits, inpatient care visits, and SCD care unit visits. Articles unavailable in English or those focused on populations outside the USA were excluded. Of the 26 articles included, 4 were prospective and the remainder were retrospective. Qualitative analysis of the articles revealed a higher rate of ED utilization among adults than children, patients with public insurance than private insurance, and patients with more comorbidities, complications, or pain. Age and pain levels were both commonly cited as predictors of ED utilization. Additional prospective and interventional studies are needed to further define predictors of ED utilization and to uncover treatments that decrease ED visits.

Keywords Emergency medicine · Sickle cell disease · Systemic literature review · Vaso-occlusive crisis

Introduction

Sickle cell disease (SCD) is a complex genetic disorder that affects multiple organ systems and is characterized by the presence of abnormal erythrocytes [1]. SCD is caused by a missense mutation in the human beta globin gene (HBB) leading to the hemoglobin variant HbS. Patients with SCD can be homozygous (HbSS) or heterozygous for the mutation (HbSC) [1]. HbS–β^0-thalassemia is a form of SCD that is clinically similar in severity to HbSS [1]. SCD predominantly affects individuals of African descent, and it is characterized by complications such as vaso-occlusion, multi-organ damage, and early death [1, 2].

It is estimated that up to 100,000 patients in the USA have SCD [2]. The life expectancy for patients with SCD has increased dramatically over the past few decades. Advancements in early diagnosis, treatments (e.g., hydroxyurea, L-glutamine, crizanlizumab, and voxelotor), blood transfusion, and hematopoietic stem cell transplantation have markedly improved outcomes [3]. However, there are still many unmet medical needs. Adherence and persistence with hydroxyurea are low, and a high rate of comorbidities complicates SCD management [4]. As such, the median life expectancies for patients with HbSS and HbSC are 58 and 66 years, respectively, which are less than the general population by 1 to 2 decades [5, 6].

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Emergency department (ED) utilization because of pain is relatively common for patients with SCD. Each year, nearly 200,000 ED visits are documented with SCD listed as a diagnosis in the USA [7]. The most common cause of pain and subsequent ED use among patients with SCD is vaso-occlusive crisis (VOC) secondary to vascular occlusion, resulting in tissue ischemia or necrosis and severe pain [7, 8]. Approximately 60% of patients with SCD require hospital-based treatment for at least one severe VOC each year. Furthermore, nearly one quarter of patients with SCD require hospital-based treatment for five or more incidences of VOC each year [9].

High reliance on the ED is not ideal because of the potential for discontinuity of care. This is particularly true for patients with SCD, which was associated with lower quality indicator scores than other chronic diseases, including asthma, heart failure, and diabetes [10]. When presenting to the ED with pain, patients with SCD often face longer wait times relative to other painful conditions [11, 12], stigma [13, 14], clinical suspicion of substance abuse [14], and inadequate analgesia [15]. ED visits are also associated with a substantial cost burden for patients with SCD. In 2006, the ED-related charges for SCD totaled $356 million; when inpatient costs are included, the total annual costs were $2.4 billion [16]. The costs for SCD-related ED visits per 100 patients are higher than those for congestive heart failure, HIV, or asthma [16]. In contrast with reliance on the ED, continuity of care is associated with better patient outcomes: lower odds of complications, lower costs, and lower rates of hospitalization [17].

A higher number of health care encounters—particularly unplanned ED visits—are associated with worse patient outcomes. For example, health-related quality of life (QoL) decreases with increasing utilization of health care services due to pain [18]. Furthermore, frequent or prolonged hospitalization is a risk factor for death among patients with SCD [19]. Over a 5-year period, the risk of mortality for patients who needed hospital-based treatment for painful VOC was 2.7-fold higher than that for patients who did not need hospital-based treatment for painful VOC [9].

It is unclear whether the poorer patient outcomes are a cause of the unplanned health care use or an effect, but it is important to understand factors that influence ED use. Despite the interest in lowering the frequency of ED visits and increasing comprehensive care among patients with SCD, many aspects of ED utilization are not well understood for this patient population. An improved understanding of predictors of ED visits may be useful for health care providers and policy makers when evaluating ways to optimize quality by reducing ED utilization. Therefore, the objective of this systematic review is to summarize the available evidence regarding the risk factors for ED visits by adults and children with SCD in the USA.

Methods

Search strategy

This systematic review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PubMed and Embase were searched for the following keywords: “sickle cell disease” AND (“emergency” OR “acute care”) AND (“utilization” OR “health care”). Publications between 1 January 2000 and 26 September 2019 were included using search filters. Reviews and case reports were excluded with PubMed and Embase filters.

Abstract review

All citations were managed in Microsoft Excel. Duplicate publications were removed. Both authors reviewed all abstracts. Inclusion criteria were as follows: initial publication date of 1 January 2000 through 26 September 2019, report of ED or acute care clinic use, and report of health care utilization. Exclusion criteria included the following: articles not available in English, case reports or review articles, and report on quality of care or outcomes without discussion of health care utilization. All discrepancies were resolved through discussions between the two authors.

Full-text review

Full-length articles were reviewed by both authors for inclusion in the systematic review. The inclusion criteria were the same as those for the abstracts, plus the following: SCD health care utilization was reported independently of other disease conditions and ED visits were reported independently of hospital admission, inpatient care visits, and SCD care unit visits. The exclusion criteria were the same as those for the abstracts, plus the following: reporting on ED re-visits or hospital readmission, not reporting risk factors or predictors for ED visits, conducted outside of the USA, and failure to evaluate risk factors pre-intervention in prospective interventional studies. Few discrepancies between the authors occurred. Discrepancies were resolved through discussions between the authors.

Data abstraction

A standardized abstraction table was used to systematically collect and summarize the following information from each included article: author name(s), publication year, title, study type (prospective, retrospective, or other), objective(s), data source(s), population, sample size, demographics, and predictors of ED use. The predictors of ED use across studies were qualitatively analyzed and categorized as related to care pathway, caregiver, demographics, health status, psychiatric, or others.

Results

Search results

As outlined in Fig. 1, a total of 451 unique records were identified with PubMed and Embase searches. Of these records, 307 were excluded on the basis of abstract review. In total, 144 full-text articles were reviewed for inclusion and exclusion criteria, and 118 publications were excluded, leaving 26 publications for data extraction of risk factors related to ED utilization (Table 1) [20–45].

Predictors of ED use

Of the 26 included publications, 4 were prospective observational trials and the remainder were retrospective studies. In these studies, the relationship between demographics, caregivers, care pathways, health status, psychiatric conditions, and ambient temperature were reported and are summarized in Table 2 [20–23, 25–31, 33, 35–38, 40, 41, 44, 45].

Demographics

Age

Determining the impact of age on ED utilization was the primary objective in three studies [22, 30, 38]. Among the studies that evaluated the effect of age on ED utilization, adulthood (age ≥ 18 years) tended to be associated with more ED utilization than childhood. However, in two separate studies, which had smaller sample sizes of less than 250 patients, age was not significantly associated with ED utilization [20, 21]. Neither of these studies included the effect of age on ED utilization as a primary outcome.

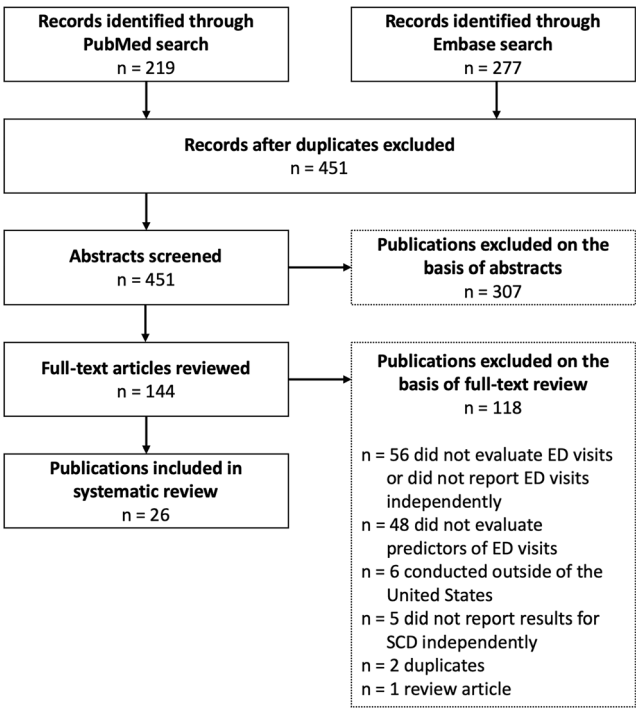

Fig. 1 Selection of studies evaluating predictors for emergency department utilization among patients with sickle cell disease

In Blinder et al., investigators evaluated the age-related patterns of ED utilization, particularly for patients transitioning from pediatric to adult care [22]. High ED utilization was defined as ED reliance (ED visits/total outpatient visits) of 0.33 [22]. For patients who were 18 years or older, the odds of high ED reliance were 2.38-fold higher than for those who were younger than 18 years ($P < 0.001$) [22]. This study also demonstrated that the cost of care for ED reliant patients is far greater than the cost of ED utilization alone as other associated costs are also increased (Table 3). Patients with high ED reliance experienced significantly higher total quarterly health care costs versus those with low ED reliance ($14,715 vs. 7339, respectively; $P < 0.001$). These higher costs were driven by inpatient costs ($10,971 vs. $3543, $P < 0.001$) and ED costs ($499 vs. 57, $P < 0.001$) despite lower outpatient costs ($781 vs. 1222, $P < 0.001$) and pharmacy costs ($816 vs. 1262, $P = 0.182$). Resource utilization trended similarly, as patients with high ED reliance versus patients with low ED reliance experienced more ED visits per quarter (4.16 vs. 0.62, $P < 0.001$), more days in an inpatient setting (4.29 vs. 1.36, $P < 0.001$), and fewer outpatient visits (2.86 vs. 4.92, $P < 0.001$).

Hemker and colleagues investigated the use of the ED during four distinct age ranges over a 5-year period: (1) childhood (age ≤ 18 years); (2) transition (turning age 19 years during study); (3) young adulthood (age 19–30 years); and (4) adulthood (age 31–45 years) [30]. Turning 19 years old or being in the age range of 19–30 years during the study period were both associated with higher ED utilization than younger or older age ranges [30]. The researchers proposed that a transition from pediatric to adult providers may lead to an increase in reliance on the ED because of limitations in access to primary care providers [30]. These findings were supported by a study published by Singh et al., in which patients who turned 19 years of age during the 5-year study period had a significantly higher likelihood of ED reliance than adults aged 31 to 45 years at the start of the study ($P = 0.007$) [40]. In this study, an ED reliance of more than 0.33 (a value that considers the proportion of ED visits versus ambulatory visits) was considered to be an over-reliance on the ED [40]. Approximately 50% of patients who transitioned during the study period had an ED reliance greater than 0.33 compared with less than 20% of patients who were 18 years or younger for the duration of the study [40].

In Sanders et al., researchers evaluated pain and health care utilization in younger adults (age 18–36 years) and older adults (age 37–62 years) [38]. Although the number of pain crises and pain level on a typical day were not significantly different between age groups, the ED visits for pain in the past year were significantly higher in younger adults (4.5 vs. 1.9 for younger

Table 1 Characteristics of included studies

Author [ref.]	Study type	Objective(s)	Data source(s)	Population	Sample size	Mean age[a] (year)	Gender[a] (% female)	Race[a] (% African American)
Aisiku et al. [20]	Prospective	To describe patients with SCD who are high utilizers of the ED and compare them with the general SCD population	Diary, survey, laboratory examination	Patients with SCD who were ≥16 years and residing in Virginia	232	34.3	61.6	NR
Badawy et al. [21]	Retrospective	To assess the relationship between participant characteristics and SCD patient-reported and clinical outcomes	Survey, medical record review	Patients with SCD aged 12–22 years who attended a comprehensive sickle cell clinic in Chicago	34	13.5	41	91
Blinder et al. [22]	Retrospective	To investigate age-related patterns of ED utilization and factors associated with high ED utilization in patients with SCD and to examine the most frequent SCD-related complications associated with ED visits	Insurance claims database	Patients with SCD and enrolled in Medicaid	3208	NR	NR	NR
Brown et al. [23]	Retrospective	To longitudinally investigate the perceptions of disease severity among children and adolescents with SCD and their caregivers and to determine whether perceptions of disease severity impacted ED use relative to objective measures of disease severity	Survey, medical record review, hospital database	Patient-caregiver pairs; patients had SCD and were between 8 and 18 years of age	58	11.8	57	100
Caldwell et al. [24]	Retrospective	To evaluate the relationship between health literacy and hospital encounters, ED visits, and hospitalizations in adolescents with SCD	Survey, medical record review	Black, non-Hispanic adolescents aged 10 to 19 years with SCD	134	14.8	53	100
Carroll et al. [25]	Retrospective	To identify demographic, medical, and psychosocial factors among patients with SCD that distinguished frequent utilizers of urgent or emergent care resources from low utilizers	Medical record review, survey, interview	Patients with SCD from the Sickle Cell Center for Adults at Johns Hopkins Hospital	56	NR	NR	NR
Curtis et al. [26]	Retrospective	To identify steady-state markers for frequent ED use	Medical record review	Adult patients with SCD from a single institution	432	NR	54	NR
Epstein et al. [27]	Retrospective	To examine the office, ED, and hospital use data for patients with SCD and evaluate the relationships between demographic and clinical characteristics and ED use	Medical record review	Patients with SCD receiving care at a single institution for ≥3 years	142	37.6	65	NR
Glassberg et al. [28]	Retrospective	To compare wheezing versus a doctor diagnosis of asthma as risk factors for SCD morbidity	Medical record review	ED patients with SCD	262	23.8	49	NR
Hafner et al. [29]	Prospective	To describe comorbid conditions in patients with SCD treated in the ED for acute pain crises and to evaluate if multiple concurrent diagnoses are a predictor of higher ED utilization and hospital admission	Medical record review	Adults with acute pain crisis and SCD who were treated in the ED	35	31.6	46	97
Hemker et al. [30]	Retrospective	To examine health care utilization patterns and reliance on ED care among patients	Insurance claims database		687	NR	NR	NR

Table 1 (continued)

Author [ref.]	Study type	Objective(s)	Data source(s)	Population	Sample size	Mean age[a] (year)	Gender[a] (% female)	Race[a] (% African American)
		with SCD transitioning from pediatric to adult care		Patients with SCD who were children or adults under the age of 45 years				
Jonassaint et al. [31]	Retrospective	To determine the association between education and ED utilization among adults with SCD	Medical record review, interview	Patients with SCD ≥ 15 years of age receiving ambulatory care at two urban hospital centers	258	35.9	NR	NR
Kamble et al. [32]	Prospective	To evaluate the prevalence of depression and its association with QoL and health care utilization	Physician billing records	Adults with SCD treated at a single center	142	34.2	57	NR
Latzman et al. [33]	Retrospective	To examine associations between frequency of ED visits, various parenting styles, and psychopathological outcomes among pediatric patients with SCD	Survey	Patients with SCD aged 6–18 years and their caregivers	98	11.2	44	100
McClish et al. [34]	Prospective	To compare reported pain, crises, health care utilization, and opioid usage between adult men and women with SCD	Diary	Patients with SCD aged ≥ 16 years	226	34	62	NR
Morrison et al. [35]	Retrospective	To determine the association between health literacy, medication knowledge, and pain treatment skills with ED use of parents of children with SCD	Medical record review, survey	Children with SCD between ages 1 and 12 years and their parents	100	NR	NR	NR
Mvundura et al. [36]	Retrospective	To describe health care utilization and expenditures by insurance status for children aged 1–17 years with SCD	Insurance claims database	Children born between 1988 and 2004 with SCD	3049	NR	NR	NR
Pantaleao et al. [37]	Retrospective	To examine relationships among caregiver psychosocial factors, cues to action, and ED utilization for their child with SCD	Medical record review, survey	Caregivers of treatment-seeking children with SCD aged 6–16 years	30	11.2	37	87
Sanders et al. [38]	Retrospective	To examine group differences in pain, coping, and health care utilization in younger and older adults with SCD	Survey	Adults with SCD from a single center	70	34.9	69	NR
Shankar et al. [39]	Retrospective	To evaluate the impact of proximity to comprehensive care centers on the health care utilization and mortality among children < 20 years of age with SCD in the state of Tennessee	Insurance claims database	Patients with SCD under the age of 20 years	1214	NR	49	NR
Singh et al. [40]	Retrospective	To estimate ED reliance in patients with SCD and to evaluate the relationship between pain, hydroxyurea use, and ED reliance	Insurance claims database	Patients with SCD in Wisconsin continuously enrolled in Medicaid or with a gap of less than 3 months	750	17.1	NR	NR
Smith et al. [41]	Retrospective	To study the relationship between weather changes and ED visits and admissions among a local SCD population	Physician billing records	ED visits for patients with SCD crisis as a primary diagnosis	256	NR	48	NR

Table 1 (continued)

Author [ref.]	Study type	Objective(s)	Data source(s)	Population	Sample size	Mean age[a] (year)	Gender[a] (% female)	Race[a] (% African American)
Stanton et al. [42]	Retrospective	To examine the effect of perceived discrimination, optimism, and their interaction on health care utilization among African American adults with SCD	Survey	Patients with SCD aged 18 years or older from a single center	49	37	71	100
Tackett et al. [43]	Retrospective	To assess whether secondhand smoke exposure among children with SCD increased ED visits	Medical records review, laboratory examination, survey	Patient-caregiver pairs; children with SCD and their caregivers	31	9.0	58	90
Vekeman et al. [44]	Retrospective	To evaluate the impact of iron chelation therapy adherence on health care resource use and costs among patients with SCD or thalassemia	Insurance claims database	Medicaid patients with SCD using iron chelation therapy	728	NR	55	NR
Wolfson et al. [45]	Retrospective	To evaluate social and demographic predictors of ED utilization in patients with SCD	Statewide database	Patients with SCD as a primary diagnosis and with an ED discharge	2920	NR	58	81

ED, emergency department; *NR*, not reported; *QoL*, quality of life; *SCD*, sickle cell disease

[a] Demographics of participants with SCD

vs. older adults; $P = 0.02$) [38]. Data from Carroll et al. support the results from the Sander study [25, 38]. Carroll and colleagues evaluated ED utilization among patients recruited from the Johns Hopkins Sickle Cell Center for Adults. These patients were considered to be in the top 10% of ED utilization and were compared with a more typical patient population [25]. Among the high-utilizing population in this study, the average age was 28.6 years, which was significantly younger than the average age of the typical use population of 38.0 years ($P = 0.002$) [25].

Gender

Gender was not significantly associated with ED usage in most studies. In McClish et al., which specifically evaluated gender differences in pain and health care utilization, no significant difference in ED use between genders was reported [34].

Education

In the studies that evaluated education and its impact on ED utilization, the results were mixed. The primary objective of Jonassaint et al. was to determine how ED utilization was affected by educational attainment [31]. In this study, 258 patients were surveyed and medical records were reviewed. The researchers reported that either a high school education or less was associated with a higher rate of ED use than post-secondary education [31]. In Carroll et al., however, a higher level of paternal education was associated with a higher utilization of the ED [25]. The researchers acknowledged that this finding was contrary with expectations and attributed the results to the relationship of parental education and greater socioeconomic status, higher access to care, and a more positive attitude toward health care [25].

Insurance

In all publications that included insurance as a variable, public insurance was associated with a higher rate of ED utilization than private insurance. In Jonassaint et al., the incidence rate ratio of ED utilization was 2.46 for public insurance relative to private insurance [31]. Similarly, Mvundura and colleagues evaluated patients with SCD from insurance claims databases and reported that compared with private insurance coverage, Medicaid coverage was associated with a higher proportion of patients with at least one ED visit (57 vs. 45%; $P < 0.01$) and a higher mean number of visits (2.4 vs. 2.0; $P < 0.01$) [36].

Clinical/disease related

Comorbidities and complications

Multiple studies evaluated the impact of health-related factors on ED utilization. Several comorbidities and complications

Table 2 Factors that significantly affected emergency department use among pediatric and adult patients with sickle cell disease

Author [ref.]	Factors associated with higher ED use
Demographics	
Blinder et al. [22]	Age > 18 years ($P < 0.001$)
Carroll et al. [25]	Age closer to young adulthood than to older adulthood ($P = 0.002$) Higher level of paternal education ($P = 0.02$)
Hemker et al. [30]	Transitioning from pediatric to adult providers[a] (turning 19 years old; $P \leq 0.01$); age 19–30 years[a] ($P \leq 0.002$)
Sanders et al. [38]	Age 18–36 years[b] ($P = 0.02$)
Wolfson et al. [45]	Age ≥ 21 years ($P < 0.01$)
Brown et al. [23]	Higher level of maternal education ($P = 0.02$)
Jonassaint et al. [31]	Lower education level ($P < 0.001$); higher level of poverty ($P < 0.001$); disability ($P < 0.001$)[c]; public insurance ($P = 0.019$)
Mvundura et al. [36]	Medicaid ($P < 0.01$)
Singh et al. [40]	Transitioning from pediatric to adult providers[a] (turning 19 years old; $P = 0.007$)
Wolfson et al. [45]	Public insurance ($P < 0.01$); greater distance to care ($P < 0.01$)
Inpatient utilization	
Blinder et al. [22]	Inpatient resource utilization in previous quarter ($P < 0.001$)
Epstein et al. [27]	Higher level of inpatient utilization ($P < 0.001$)
Parent/caregiver-related	
Latzman et al. [33]	Authoritarian parenting style ($P < 0.05$)
Morrison et al. [35]	Caregiver unable to recall medications ($P < 0.05$); caregiver underdosing in dosage or frequency ($P < 0.05$); caregiver underdosing in frequency ($P < 0.05$)
Pantaleao et al. [37]	Caregiver stress frequency ($P < 0.05$); stress related to communication with child or medical team ($P < 0.05$); stress related to medical care frequency ($P < 0.05$)
Clinical/disease-related	
Aisiku et al. [20]	Lower hematocrit level ($P < 0.003$); worse pain (pain days, pain crises, and pain and distress; all $P < 0.05$)
Blinder et al. [22]	SCD complication in current quarter ($P < 0.001$); COPD in previous quarter ($P = 0.01$); pregnancy complication in previous quarter ($P < 0.001$)
Curtis et al. [26]	Higher steady-state WBC levels ($P < 0.001$); higher steady-state platelet count ($P < 0.001$); lower steady-state RBC count ($P < 0.001$); lower steady-state hemoglobin ($P < 0.001$)
Glassberg et al. [28]	Asthma[d] ($P = 0.04$); wheezing[d] ($P < 0.001$)
Hafner et al. [29]	Higher number of concurrent ICD-9 codes ($P < 0.001$)
Vekeman et al. [44]	Nonadherence to iron chelation therapy ($P < 0.001$)
Wolfson et al. [45]	Worse disease severity ($P < 0.01$)
Badawy et al. [21]	Chronic pain ($P = 0.04$)
Jonassaint et al. [31]	Daily pain ($P < 0.001$)
Brown et al. [23]	Higher child-reported friendship quality ($P < 0.01$); higher child-reported subjective perception of disease severity ($P = 0.03$)
Carroll et al. [25]	Higher family history of psychiatric illness ($P < 0.05$)
Jonassaint et al. [31]	Psychiatric diagnosis ($P = 0.042$)
Latzman et al. [33]	Socially withdrawn or other signs of depression in children ($P < 0.05$)
Treatments	
Aisiku et al. [20]	Transfusion in last 3 months ($P < 0.003$)
Blinder et al. [22]	Pain medication use in current quarter ($P < 0.001$); transfusion in current quarter ($P < 0.001$)
Singh et al. [40]	Hydroxyurea possession ($P = 0.01$)
Quality of life	
Aisiku et al. [20]	Lower physical subdomain scores on the SF-36 ($P < 0.003$)
Temperature	
Smith et al. [41]	Temperatures below 0 °C (32 °F) ($P < 0.001$); change in temperature from 24 h prior to encounter ($P < 0.001$); change in temperature from 48 h prior to encounter ($P < 0.001$)

COPD, chronic obstructive pulmonary disorder; *ED*, emergency department; *ICD-9*, International Classification of Diseases, 9th Revision; *RBC*, red blood cell; *SCD*, sickle cell disease; *SF-36*, 36-Item Short Form Health Survey; *WBC*, white blood cell

[a] Associated with higher ED use relative to children aged ≤ 18 years and adults aged 31–45 years during a 5-year period

[b] Associated with higher ED use relative to adults aged 37–62 years

[c] Associated with higher ED use relative to adults aged 31–45 years

[d] Only included ED visits for painful episodes

were associated with an increased risk of ED utilization. Hafner and colleagues performed a medical record review of 35 patients with SCD and found that a higher number of co-morbidities (measured on the basis of International Classification of Diseases, 9th Revision [ICD-9], codes) were associated with a higher frequency of ED visits [29]. Similarly, in a review of 3208 patients from a Medicaid claims database, Blinder and colleagues reported that SCD

Table 3 Quarterly health care costs and resource utilization for patients with high vs. low emergency department reliance [22]

	Low EDR (≤ 0.33) (A)	High EDR (> 0.33) (B)	Difference B-A	*P* value
Total quarterly costs ($, mean ± SD)	7339 ± 13,345	14,715 ± 20,650	7376	< 0.0001
Before 18 years old	5983 ± 11,949	9615 ± 14,737	3633	< 0.0001
After 18 years old	9118 ± 14,793	17,238 ± 22,600	8121	< 0.0001
Inpatient quarterly costs ($, mean ± SD)	3543 ± 10,612	10,971 ± 18,272	7427	< 0.0001
Before 18 years old	2554 ± 9110	7352 ± 12,329	4798	< 0.0001
After 18 years old	4841 ± 12,187	12,762 ± 20,352	7920	< 0.0001
ED quarterly costs ($, mean ± SD)	57 ± 246	499 ± 1665	442	< 0.0001
Before 18 years old	35 ± 197	191 ± 831	157	< 0.0001
After 18 years old	85 ± 296	651 ± 1931	566	< 0.0001
Outpatient quarterly costs ($, mean ± SD)	1222 ± 2764	781 ± 2004	− 441	< 0.0001
Before 18 years old	1207 ± 2610	510 ± 1502	− 697	< 0.0001
After 18 years old	1243 ± 2952	915 ± 2199	− 328	< 0.0001
Pharmacy quarterly costs ($, mean ± SD)	1262 ± 3221	816 ± 2069	− 447	0.1819
Before 18 years old	981 ± 2583	330 ± 1114	− 651	< 0.0001
After 18 years old	1632 ± 3873	1056 ± 2369	− 576	< 0.0001
ED visits per quarter (mean ± SD)	0.62 ± 1.35	4.16 ± 5.66	3.54	< 0.0001
Before 18 years old	0.40 ± 0.84	2.46 ± 3.17	2.06	< 0.0001
After 18 years old	0.91 ± 1.77	5.00 ± 6.39	4.10	< 0.0001
Days in the hospital per quarter (mean ± SD)	1.36 ± 3.87	4.29 ± 8.41	2.93	< 0.0001
Before 18 years old	0.87 ± 2.69	2.00 ± 3.27	1.13	< 0.0001
After 18 years old	2.01 ± 4.95	5.43 ± 9.82	3.42	< 0.0001
Days with an outpatient visit per quarter (mean ± SD)	4.92 ± 5.99	2.86 ± 4.64	− 2.06	< 0.0001
Before 18 years old	4.15 ± 4.55	1.82 ± 2.42	− 2.33	< 0.0001
After 18 years old	5.93 ± 7.34	3.38 ± 5.34	− 2.55	< 0.0001

Emergency department reliance (EDR) was defined as the number of emergency department (ED) visits divided by the sum of ED and outpatient visits in the quarter. High EDR was defined as EDR > 0.33. Patients were classified as low EDR or high EDR based on individual quarters of observation and were able to be in different groups in subsequent quarters

complications were associated with significantly higher odds of high ED reliance (odds ratio (OR), 4.18; $P < 0.001$), as was comorbid chronic obstructive pulmonary disease (OR, 1.14; $P = 0.01$) [22]. Intriguingly, both cerebrovascular disease (OR, 0.75; $P < 0.001$) and pregnancy complications (OR 0.53; $P < 0.001$) were negatively correlated with ED utilization [22].

In Glassberg et al., the impact of wheezing and asthma on ED utilization by patients with SCD was evaluated, and both wheezing and asthma were independently associated with an increased rate of ED utilization for painful episodes. The rate ratio for asthma was 1.44 ($P = 0.04$), and for wheezing, it was 2.18 ($P < 0.001$) [28].

Steady-state laboratory values

In Curtis et al., researchers evaluated the impact of steady-state laboratory values on health care utilization, with the goal of identifying biomarkers for frequent ED use to target patients for treatment [26]. The authors stratified patients by number of annual visits: 0–1, 2–5, or ≥ 6 ED visits [26]. In the steady state, higher ED utilization was associated with higher white blood cell levels, higher platelet counts, lower red blood cell counts, lower hemoglobin levels, and lower albumin levels [26]. These values were linearly and statistically significantly associated with ED utilization [26].

Pain

Chronic pain was also a predictor of ED utilization. In Aisiku et al., a higher number of pain days, a higher number of pain crises, and higher mean pain scores were clinically significantly associated with high ED utilization among patients with SCD, which was defined as three or more ED visits per year [20]. In a single-center, cross-sectional study of young patients with SCD, chronic pain was associated with a

significantly higher rate of ED visits ($P = 0.04$) [21]. Finally, in Jonassaint et al., daily pain was associated with an increased incident rate of ED visits by 2.15 ($P < 0.001$) [31].

Psychiatric conditions

More psychiatric illness (either familial or personal history) appeared to be associated with a higher level of ED utilization in several studies. Psychiatric illness in the immediate family occurred significantly more frequently among high utilizers (42.9%) than typical utilizers (7.41%; $P = 0.007$) in the retrospective medical record review by Carroll et al. [25]. Furthermore, the presence of a psychiatric diagnosis was associated with 1.95-fold higher incidence rate ratio of ED visits ($P = 0.04$) in the study by Jonassaint et al. [31]. In Stanton et al., which specifically evaluated the relationship between optimism and health care utilization in patients with SCD, perceived discrimination and optimism interacted with but were not significantly associated with the number of ED visits ($P = 0.052$) [42]. Furthermore, in a meeting abstract from 2010, depression was not associated with SCD ED visits [32].

Parent or caregiver

Several studies enrolled caregiver-child pairs to evaluate the impact of parent and caregiver factors on ED utilization. In Latzman et al., a total of 98 caregiver/patient pairs were enrolled and completed surveys regarding parenting style, child psychopathology, and ED visit frequency [33]. Authoritarian parenting style (i.e., use of physical punishment) was positively associated with ED visits; authoritative parenting (i.e., responsive to feelings and needs) and permissive parenting (i.e., difficulty with disciplining) were not associated with ED visit use [33]. Furthermore, Pantaleao and colleagues reported that caregiver stress frequency was associated with higher ED utilization [37].

To evaluate the associations between caregiver health literacy and child ED usage, Morrison et al. evaluated the medication knowledge and skills of 100 caregivers of children with SCD [35]. A caregiver's inability to recall the medications that child was receiving was associated with significantly more ED usage [35]. Furthermore, underdosing was measured both by knowledge of dose and frequency and with an applied skills task requiring caregivers to administer a prescribed dosage. Both a lack of knowledge and a lack of applied skills leading to underdosing were associated with increased ED utilization [35].

In contrast, a study by Caldwell et al. showed no significant relationship between health literacy and ED visits [24]. The authors noted that demographic differences that could lead to this discrepancy with past studies included a lower inpatient hospitalization rate compared with national samples as well as the study population, who were part of a comprehensive SCD treatment program with a clinic and a day hospital. It is possible that some patients were diverted from ED use through these programs [24].

Quality of life

Health-related QoL was evaluated as a risk factor for ED use in one study. The physical component of the health-related QoL 36-Item Short Form (SF-36) survey negatively predicted the rate of ED utilization, meaning a higher SF-36 score was associated with lower ED use. There was no significant association for the SF-36 mental component [20].

Treatments

An increased rate of hydroxyurea possession was associated with a decreased rate of ED reliance, according to the analysis of the Wisconsin Medicaid SCD population in Singh et al. [40]. Of note, this correlation persisted for all SCD age groups [40].

Transfusion history is another predictor of the rate of ED utilization. In Aisiku et al., transfusion in the past 3 months was associated with a higher rate of ED utilization [20]. Intriguingly, Blinder and colleagues reported that transfusion in the current quarter was associated with a higher rate of ED utilization, whereas transfusion in the previous quarter was associated with lower odds of high ED utilization [22]. The authors hypothesized that the receipt of a transfusion in the current quarter may be indicative of acute interventions consistent with ED utilization, whereas receipt of transfusion during the previous quarter may be indicative of preventive treatment, which would lower the use of the ED [22].

Inpatient utilization

In the two studies that evaluated inpatient resource utilization and ED use, a positive correlation was reported. Epstein and colleagues evaluated the health care resource use of 142 patients from a single institution [27]. Approximately 20% of the highest inpatient utilizers accounted for 54% of the total ED visits [27]. Inpatient utilization was significantly associated with independent ED use (i.e., ED visits that did not result in hospital admission) [27]. Similarly, in Blinder et al., inpatient resource utilization was associated with high ED use (OR, 1.026; $P < 0.001$) [22].

Care pathway

Shankar and colleagues compared the rates of ED visits within a region with a comprehensive SCD care center and regions without such a center [39]. While the rates of ED visits across regions were not significantly different, the ED visit rates were numerically higher for patients living in a region without access to a comprehensive care center [39].

Temperature

Ambient temperature has long been believed to impact the occurrence of VOCs and pain among patients with SCD. In Smith et al., the impact of temperature on ED visit frequency was evaluated [41]. They reported that ambient temperatures less than 0 °C (32 °F) were positively and clinically significantly correlated with ED visits; temperatures over 26 °C (80 °F) were negatively statistically significantly (but not clinically significantly) associated with ED visits [41]. Furthermore, change in temperature 24–48 h prior to an ED visit was significantly associated with the number of ED visits [41].

Discussion

We have qualitatively summarized some trends across the evaluated studies in this systematic literature review. In most of the studies evaluated here, age was associated with ED use. There appears to be an inverted U-shaped age trend for ED use: ED utilization was lower in childhood and in older adults and was higher in younger adults [22, 30, 38, 40]. Compared with children, adults were shown to have a higher rate of ED visits and were also more likely to be a part of the high utilization group [45]. Although the reason for the trend in age is unclear, Hemker et al. and Singh et al. hypothesized that transition from pediatric to adult care providers may lead to ED utilization as a primary care service provider caused by care fragmentation, a delay in arranging care with an adult care facility, or the challenging shift in disease management responsibilities from the caregiver to the patient [30, 40, 46]. This hypothesis is supported by the findings of Sanders et al., who reported that the number of pain crises and pain levels on a typical day are not significantly different between age groups, but the rates of ED visits for pain are nonetheless higher among adults [38], suggesting that disease and/or pain severity are not directly correlated with the increased use of EDs among adults relative to children. However, in a retrospective study of patients with SCD, the authors reported that opioid use increased with increasing age [47]. It is difficult to determine whether opioid use is more common in adults due to higher levels of pain or for other reasons (e.g., transition from pediatric to adult care), but patients who received opioids were more likely to have VOCs, suggesting a link between opioid use and pain. Furthermore, poor acute pain treatment response has been associated with higher use of an acute care center and higher baseline opioid use, suggesting a complex association between age, opioid use, chronic and acute pain, response to pain treatment, and acute care utilization [48]. More prospective trials that control for multivariate confounders are needed to determine what factors drive the relationship between age and ED utilization.

The Examining Sickle Cell Acute Pain in the Emergency vs. Day Hospital (ESCAPED) trial is an ongoing prospective study that is evaluating the outcomes of patients with SCD who have attended a specialty infusion clinic or ED for acute pain management. In an early report of the baseline characteristics and health care utilization of these patients, the following factors were associated with higher rates of acute care utilization: unemployment, chronic pain, chronic transfusion therapy, history of stroke, disability, or Medicaid [49]. Many of the predictors of acute care utilization discussed in this prospective study are in line with the risk factors for ED utilization reported in this review.

A complete understanding of risk factors for ED utilization among patients with SCD is important because some variables may be modifiable through provider or health care policy interventions. Interviews of patients visiting the ED for VOC have revealed several factors associated with the decision to use the ED: difficulty with transportation to clinics, scheduling conflicts, insurance coverage issues, and difficulties obtaining prescriptions [50].

If a lack of access to care is influencing ED utilization, such as in the case of elevated utilization during transition ages, it is possible that increased access to comprehensive care centers may improve transitional care. Although SCD is more common than other genetic disorders (e.g., cystic fibrosis and hemophilia), access to comprehensive specialized care for patients with SCD is limited [51]. In a study published in 2000, a day hospital was established to provide analgesic care for patients with uncomplicated painful VOCs. Within the first 5 years of the opening of the day hospital, the rate of ED admissions dropped by 40%, suggesting that patients with uncomplicated VOCs are receiving adequate analgesia and care at the day hospital, obviating the need for ED visits [52]. However, in Shankar et al., residence in a region with a comprehensive care center was not associated with a statistically significant lower rate of ED visits [39]. This could be attributed to other access issues, including transportation difficulty, limited hours, or insurance issues. Nonetheless, a prospective study of the utility of comprehensive care centers may be warranted.

In past studies, there has been some success with directly addressing factors related to the highest rates of ED utilization on an individual basis. One fifth of patients with SCD account for over half of all SCD ED visits [53]. In a small pilot study, "super-utilizers" (mean, 38.4 ED visits/year) received individualized care plans developed by an interdisciplinary SCD committee. The individual care plans included information

on pain management and patient history [53]. After implementation of the care plans, the annual mean visits decreased to 16.5 visits/year [53]. Similarly, in a study of 242 patients, an individual care plan developed by a multidisciplinary team was associated with a reduction in ED utilization from 3.7 to 2.1 ED visits/year [54]. In both studies, the individual care plans were administered concurrently with educational interventions for providers and staff [53, 54].

Institution-wide interventions have also been shown to significantly reduce health care resource use and improve patient outcomes. In a single-institution study, a quality-improvement plan was developed that included individualized home pain plans, ED and inpatient order sets, psychoeducation, and targeted interventions for high-risk and at-risk individuals with three or more admissions per year. After the implementation of this program, hospital days decreased by 61% and the 30-day readmission rate decreased from 33.9 to 19.4%. Importantly, the overall savings in direct costs to the hospital was $555,120/year [55].

One potential limitation of the systematic review is that the majority of the studies evaluating ED utilization risk factors for patients with SCD were retrospective or prospective observational studies. More high-quality (i.e., prospective interventional) studies would be needed to evaluate predictors of ED utilization.

Conclusions

To reduce the high rate of ED utilization by patients with SCD, a number of clinical and research priorities must be addressed. First, prospective studies evaluating the risk factors for ED utilization should be conducted to determine the risk factors for high ED utilization. Second, interventional studies are needed to determine what types of treatments will decrease ED use and improve quality of care for patients with SCD. Third, patients with SCD that do use the ED for care should receive adequate analgesia and referral to a provider for prophylactic and preventive care to reduce the re-use of EDs.

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Author contributions SKB and CD independently performed the literature search and agreed on the final study selection. Both authors extracted data from the selected studies. They also assessed the quality of the included studies and performed a cross-check for data accuracy. Both authors contributed to the writing of the manuscript, and both authors approved the final manuscript.

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Data availability Data are available upon request from corresponding author.

Compliance with ethical standards

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