Received: 17 November 2020 | Revised: 26 November 2020 | Accepted: 29 November 2020

DOI: 10.1002/ajh.26063

RESEARCH ARTICLE

Impact of sickle cell disease on patients' daily lives, symptoms reported, and disease management strategies: Results from the international Sickle Cell World Assessment Survey (SWAY)

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Funding information
Novartis

Abstract

Sickle cell disease (SCD) is a genetic disorder, characterized by hemolytic anemia and vaso-occlusive crises (VOCs). Data on the global SCD impact on quality of life (QoL) from the patient viewpoint are limited. The international Sickle Cell World Assessment Survey (SWAY) aimed to provide insights into patient-reported impact of SCD on QoL. This cross-sectional survey of SCD patients enrolled by healthcare professionals and advocacy groups assessed disease impact on daily life, education and

work, symptoms, treatment goals, and disease management. Opinions were captured using a Likert scale of 1-7 for some questions; 5-7 indicated "high severity/impact." Two thousand one hundred and forty five patients (mean age 24.7 years [standard deviation (SD) = 13.1], 39% ≤18 years, 52% female) were surveyed from 16 countries (six geographical regions). A substantial proportion of patients reported that SCD caused a high negative impact on emotions (60%) and school achievement (51%) and a reduction in work hours (53%). A mean of 5.3 VOCs (SD = 6.8) was reported over the 12 months prior to survey (median 3.0 [interquartile range 2.0-6.0]); 24% were managed at home and 76% required healthcare services. Other than VOCs, fatigue was the most commonly reported symptom in the month before survey (65%), graded "high severity" by 67% of patients. Depression and anxiety were reported by 39% and 38% of patients, respectively. The most common patient treatment goal was improving QoL (55%). Findings from SWAY reaffirm that SCD confers a significant burden on patients, epitomized by the high impact on patients' QoL and emotional wellbeing, and the high prevalence of self-reported VOCs and other symptoms.

1 | INTRODUCTION

Sickle cell disease (SCD) is an inherited autosomal recessive disorder caused by a mutation in the β-globin gene and affects millions of people globally.[1,2] The disease is most prevalent in sub-Saharan Africa, India, and the Mediterranean area, but is also seen in wider Europe and the Americas.[3]

Sickle cell disease is characterized by chronic hemolytic anemia, organ damage, and vaso-occlusive crises (VOCs), which are acutely painful events. The condition can also lead to progressive damage to many end organs. Vaso-occlusive crises are the primary cause of hospital admissions in SCD, and are associated with early mortality.[4,5] The life expectancy of patients with SCD has increased in high-resource countries, such as the USA.[2,6,7] In 1994, the median age at death for males and females was 42 and 48 years, respectively.[8] In 2019, the median age at death was 48.0 years for HbSS, HbSβ^0, and HbSD disease, and 54.7 years for HbSC and HbSβ^+ disease.[9] Unfortunately, this has not been replicated in low-resource countries, where the 5-year mortality for patients aged <5 years remains high.[2]

Sickle cell disease has a significant negative effect on quality of life (QoL), due to the impact on physical and mental health, social life, work, and school.[10-15] In the absence of fully validated SCD-specific questionnaires, QoL studies have relied on standardized, generic health-related quality of life (HRQoL) assessments, such as the 36-Item Short-Form Health Survey (SF-36) questionnaire and the Pediatric Quality of Life Inventory (PedsQL).[12-17] These studies have shown that patients with SCD experience very poor HRQoL. However, these generic scales do not consider SCD-specific symptoms and are not comprehensive assessments of all aspects of patients' lives; therefore, they may underestimate the true burden of illness of SCD. Furthermore, prior HRQoL studies are also largely individual country analyses. No studies to date have examined overall burden of SCD globally.

Understanding patient-reported impact of SCD on health and wellbeing, in addition to patients' views on how their disease is treated and managed, is critical to better identify unmet needs, address barriers to care, challenge misconceptions, and improve QoL. The international Sickle Cell World Assessment Survey (SWAY) aimed to provide real-world global insights into patients' views of the impact of SCD on their daily lives and the treatment they receive.

2 | METHODS

A multi-country, cross-sectional survey across six geographical regions assessing the impact of SCD on children, adolescents, and adults, from both the viewpoint of the patient and that of healthcare professionals (HCPs), SWAY, was developed by a global steering committee including 14 SCD expert physicians and three patient advocacy group (PAG) stakeholders, with input from Novartis representatives. The primary focus of SWAY was to assess the overall disease burden rather than HRQoL alone. In the absence of a fully validated SCD-specific HRQoL instrument or single HRQoL assessment tool that measures all aspects of SCD-related disease burden, the steering committee chose to use a health burden survey approach.[18-20] The steering committee was central to the design of the SWAY health burden survey and was responsible for endorsing the research objectives and ensuring that the question wording and response options included were appropriate for the intended audience. Published global disease burden surveys have used this methodology,[18-20] and were the basis for initial question development in SWAY.[18] Questions were subsequently revised in an iterative manner based on knowledge gaps raised by the steering committee, with PAG members ensuring that the patient's viewpoint was taken into account.

Prior to circulation of the final survey, the questionnaire was piloted in a small group of respondents to validate the approach and

identify any potential problems (eg, possible ambiguous wording) with the questions and response options. No issues were identified during this pilot. Data collection and subsequent analyses were managed by Adelphi Real World (ARW).

2.1 | Objectives

The international Sickle Cell World Assessment Survey (SWAY) was designed to assess patients' experience of the impact of SCD on their daily lives. Effects on daily activities, relationships, education, and employment, as well as the emotional burden of SCD, were examined. In addition, the survey evaluated aspects of disease burden, including patient self-reported incidence of VOCs and other symptoms. Patients' treatment goals and satisfaction with current SCD treatments were also assessed. Finally, patients' opinions of overall disease management were captured.

2.2 | Participants

Patients with SCD (target: 2000 patients) and HCPs (target: 300 HCPs) were surveyed. The patient and HCP populations and survey questions were independent of one another. Patient inclusion and exclusion criteria are described in Figure S1. Patients aged 6-11 years required a proxy - a parent, guardian, or caregiver - to complete the survey. Patients aged ≥12 years could choose to complete the survey independently, with assistance or input from a parent, guardian, or caregiver, or a proxy could complete the survey. Adult patients (≥18 years) who completed the survey via proxy did not have to meet specific criteria. Patients (or their proxy) and HCPs completed the questionnaires either online or on paper (country dependent). Patient-reported and proxy-reported data are included in this paper; HCP survey data will be reported in a separate publication. Patient genotypes were self-reported and not verified against clinical records in which genotypes had been determined.

2.3 | Recruitment

Patients were recruited through treating HCPs and PAGs. The HCPs recruited both newly referred and existing patients on a consecutive basis, during routine consultations. The PAGs recruited the majority of patients by email; all members of the patient group were notified of the survey and invited to participate. Patients recruited via PAGs were screened for eligibility after being invited and were subsequently provided with a hyperlink to access the survey online. The eligibility criteria for patients are described in Figure S1. Paper surveys were only available to HCP-recruited patients in Lebanon and the Kingdom of Saudi Arabia. Responses were anonymized and no personal identifiable information was collected.

2.4 | Survey questions

Questions were developed with input from the steering committee, ARW, and Novartis. Materials were developed in English, proof-read by local fieldwork partners, and translated into local language as necessary by an accredited translation agency. All translated surveys were proof-read by a native speaker. The full list of questions is included in the supplementary material.

Patients were invited to provide a response for every question, although "not applicable" and "do not know" response options were provided where appropriate.

For some questions, patients were asked to rank their responses to statements on a 7-point Likert scale where respondents recorded the extent of their agreement with a statement. The meaning of the extremes on the scale was defined for each question. For example, 1 = "not at all" and 7 = "a great deal," 1 = "strongly disagree" and 7 = "strongly agree," or where questions related to symptom severity, 1 = "not severe at all" and 7 = "worst imaginable." In all cases, a response score of 5, 6, or 7 was deemed to be an indication of "high impact," "high severity," or "strong agreement" depending on how the scale was defined. Patients scoring 5-7 on given statements were considered to feel that SCD had a significant negative impact with respect to these statements relating to disease burden. The validity of the Likert scale as a quantifier of response, similar to a visual analog scale, has been demonstrated in studies of other conditions (such as dyspepsia). In rheumatoid arthritis, Likert scales are used to assess symptom severity as part of the American College of Rheumatology response criteria.[21-23]

2.5 | Data collection and analysis

The survey took approximately 30 minutes to complete and could only be completed once. Analyses were descriptive in nature and used STATA statistical software version 16.0. The VOCs were analyzed separately from other symptoms.

To analyze potential differences in the data reported according to country economic status, countries were designated either a high-income (HI) or low-middle-income (LMI) status. The World Bank definition for an HI economy (gross national income per capita of ≥US $12 536) was used to stratify countries.[24]

Fisher's exact (FE) or Mann-Whitney *U* (MW) tests were used to assess the relationship between the top three most commonly reported symptoms (excluding VOCs) and patient-reported high impact of SCD on daily life, emotional wellbeing, employment, and schooling. The FE test was used when comparing two binary variables, and the MW test when comparing an ordered categorical variable with a binary variable. Spearman's rank correlation coefficient was used to correlate self-reported VOC frequency with patient-reported high impact of SCD on daily life, emotional wellbeing, employment, and schooling.

3 | RESULTS

3.1 | Demographics

A total of 2145 patients were surveyed from 16 countries across six geographical regions (Figure S2) between 3 April 2019 and 4 October 2019. Of these, 1246 (58%) were recruited by HCPs via the ARW network and 899 (42%) by PAGs. Of the 2145 patients surveyed, 1204 were considered to be from HI countries (Bahrain, Canada, France, Germany, Italy, the Netherlands, Oman, Panama, Saudi Arabia, the USA, and the UK) and 941 were from LMI countries (Brazil, Ghana, India, Nigeria, and Lebanon). The mean age of patients overall was 24.7 years (standard deviation [SD] = 13.1, range 6-90 years), and 52% were female. The mean age of patients in HI countries was higher (28.6 years [SD = 13.1, range 6-90 years] than those in LMI countries (19.6 years [SD = 11.1, range 6-90 years]). The median age of patients in HI countries was 29.0 years (interquartile range [IQR] 18.0-37.0) compared with 17.0 years in LMI countries (IQR 11.0-26.0). In HI countries, 56% of patients were female, compared with 47% in LMI countries. Overall, 39% (n = 827/2144) of patients were ≤18 years old (Table 1); 25% (n = 304/1204) in HI countries, and 56% (n = 523/940) in LMI countries. Median age of patients ≤18 years old was 12.0 (IQR 9.0-15.0) years and >18 years old was 31.0 (IQR 25.0-38.0) years.

The survey was self-completed by 1461/2145 patients (68%: HI, n = 920/1204 [76%]; LMI, n = 541/941 [57%]) and completed by proxy (parent/caregiver/guardian) for the remaining 684 (32%: HI, n = 284/1204 [24%]; LMI, n = 400/941 [43%]). The majority (n = 569/683; 83%) of surveys completed by proxy were for patients ≤18 years old.

Altogether, 1632 (76.1%) patients reported that they were aware of their genotype (HI, n = 973 [81%]; LMI, n = 659 [70%]). The genotype options included in the survey for self-reporting are given in Table 1.

3.2 | Impact of sickle cell disease (SCD) on daily life

Figure 1A illustrates the proportion of patients reporting a high impact of SCD (Likert score 5-7) on various activities of daily life. For example, of the 2145 patients surveyed (HI, n = 1204; LMI, n = 941), 38% (n = 817: HI, n = 520 [43%]; LMI, n = 297 [32%]) reported that SCD impacted on their ability to perform household daily activities (food preparation, housework, gardening, oral hygiene, and taking care of children), 41% (n = 870: HI, n = 530 [44%]; LMI, n = 340 [36%]) reported that SCD affected their family or social life, while 62% (n = 1321: HI, n = 823 [68%]; LMI, n = 498 [53%]) reported that they avoided intense exercise. Of 1376 adult patients surveyed, 32% (n = 441) reported that SCD had an impact on their relationship with their spouse/partner; 36% (n = 330/927) in HI countries and 25% (n = 111/449) in LMI countries.

3.3 | Emotional wellbeing

Sixty percent (n = 1277/2145) of survey participants reported that SCD had a high impact on emotional wellbeing (Likert score 5-7), specifically frustration with symptoms (n = 1246, 58%) and worry that their disease would worsen (n = 1241, 58%) (Figure 1B). The reported

TABLE 1 Patient demographics

	Number of patients			Percentage of patients		
Genotype/age	Overall	HIC	LMIC	Overall	HIC	LMIC
Self-reported genotype (N = 2145)						
SS	1042	637	405	64%	65%	61%
SC	446	229	217	27%	24%	33%
Sβ+	60	50	10	4%	5%	2%
$S\beta^0$	54	43	11	3%	4%	2%
Other[a]	30	14	16	2%	1%	2%
Unknown	513	231	282	24%	19%	30%
Age category, y (N = 2144)[b]						
6-12	447	151	296	21%	13%	31%
13-18	380	153	227	18%	13%	24%
19-25	383	204	179	18%	17%	19%
26-35	486	339	147	23%	28%	16%
36-45	316	254	62	15%	21%	7%
≥46	132	103	29	6%	9%	3%

Abbreviations: HI, high-income countries; LMIC, low-middle-income countries.

[a]Other not specified.

[b]Age not specified, n = 1 (0.04%).

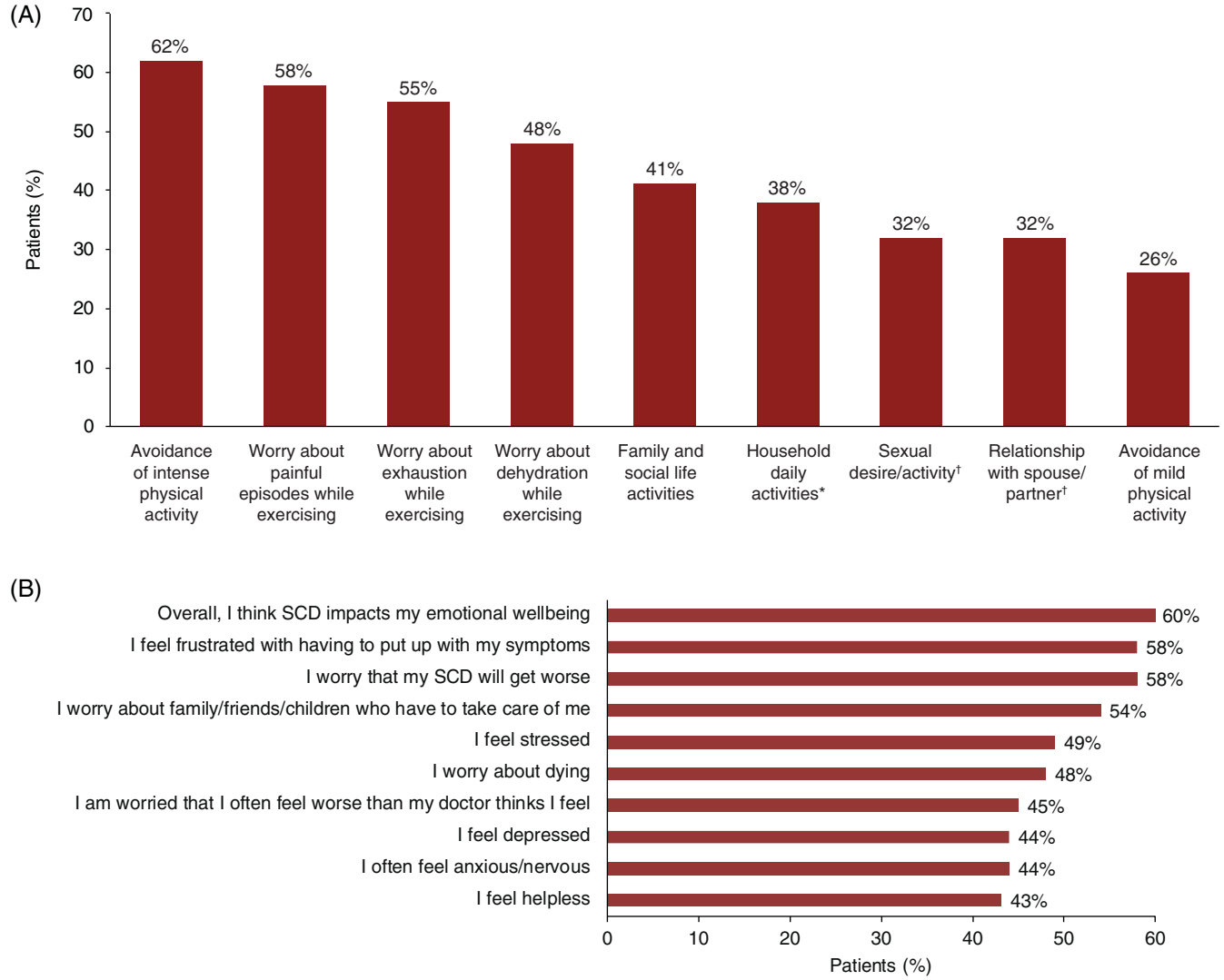

FIGURE 1 Impact of sickle cell disease (SCD) on daily life, A, and emotional impact of SCD, B, (N = 2145). A, The percentages show the proportion of patients reporting the effect of SCD on the given activity, relationship, or statement as high impact (Likert score 5-7). *Food preparation, housework, gardening, oral hygiene, and taking care of children. †N = 1376 (patients aged ≥18 years). B, The percentages show the proportion of patients reporting the effect of their SCD on the statement as having high impact (Likert score 5-7)

impact of SCD on emotional wellbeing was higher in HI countries (n = 770/1204, 64%) than in LMI countries (n = 507/941, 54%). In HI countries, 67% (n = 808/1204) and 63% (n = 759/1204) of patients reported frustration with symptoms and worry that their disease would worsen, respectively, compared with 47% (n = 438/941) and 51% (n = 482/941) in LMI countries. Similar proportions of patients rated their level of agreement with the statements "I feel stressed" and "I worry about dying" as being in the "high impact" range: 49% (n = 1048: HI, n = 622 [52%]; LMI, n = 426 [45%]) and 48% (n = 1024: HI, n = 606 [50%]; LMI, n = 418 [44%]) of patients, respectively. There was no difference across age groups in the proportion of patients rating the statement "I worry about dying" as high impact. Around a third (n = 774/2145, 36%) of patients received professional emotional support from a psychiatrist, psychologist, or counselor, and 62% (n = 1336/2145) of patients reported a desire either to start receiving professional emotional support (n = 761/1336, 57%) or to receive more of this type of support (n = 575/1336, 43%). Considerably fewer patients in HI (n = 389/801, 49%) vs LMI (n = 372/569, 65%) countries reported a desire to start receiving professional emotional support and to receive more of this type of support if already being received (HI, n = 253/403 [63%]; LMI, n = 322/371 [87%]).

3.4 | Employment history and impact of SCD on careers

There were 1728 patients eligible to complete this part of the survey; 1064 from HI countries and 664 from LMI countries. Overall, only 33% (n = 570) of patients were employed (either full-time or part-time); 42% (n = 445) in HI countries and 19% (n = 125) in LMI countries. Of the remaining eligible patients, 35% (n = 598: HI, n = 237 [22%]; LMI, n = 361 [54%]) were students, 25% (n = 439: HI, n = 324 [30%]; LMI,

n = 115 [17%]) were not working, 3% (n = 44: HI, n = 23 [2%]; LMI, n = 21 [3%]) were homemakers, and 1% (n = 20: HI, n = 14 [1%]; LMI, n = 6 [1%]) were retired. Employment circumstances are displayed in full in Figure S3A. Of those currently or previously employed, 53% (n = 509/968) of patients had reduced their working hours and 32% had been dismissed from their jobs because of their SCD (Figure S3B). Compared with LMI countries, more patients in HI countries had reduced their working hours (HI, n = 425/746 [57%] vs LMI, n = 84/222 [38%]) and had been dismissed from their jobs because of their SCD (HI, n = 260/746 [35%] vs LMI, n = 51/222 [23%]).

Of those working (N = 572), patients had missed an average of 7.0 hours (SD = 14.8) of work because of SCD in the 7 days before survey completion: 5.9 (SD = 11.8) and 10.6 (SD = 22.2) hours in HI (n = 447) and LMI (n = 125) countries, respectively. Patients reported that SCD had a substantial impact (Likert score 5-7) on their careers, as shown in Figure 2A, and 54% (n = 1164/2145) reported that they thought their income would be higher if they did not have SCD. More patients in HI countries thought that their income would be higher if they did not have SCD (n = 717/1204, 60%) than did patients in LMI countries (n = 447/941, 48%).

3.5 | Impact of SCD on schooling

Of 1376 patients aged ≥18 years who completed this part of the survey (median age 30.0 years, IQR 24.0-38.0), 51% (n = 704) reported that SCD had a high impact (Likert score 5-7) on achievement at school, and 41% (n = 564) stated that SCD decreased motivation at school. A higher proportion of patients in HI countries (n = 522/927, 56%) vs LMI countries (n = 182/449, 41%) reported

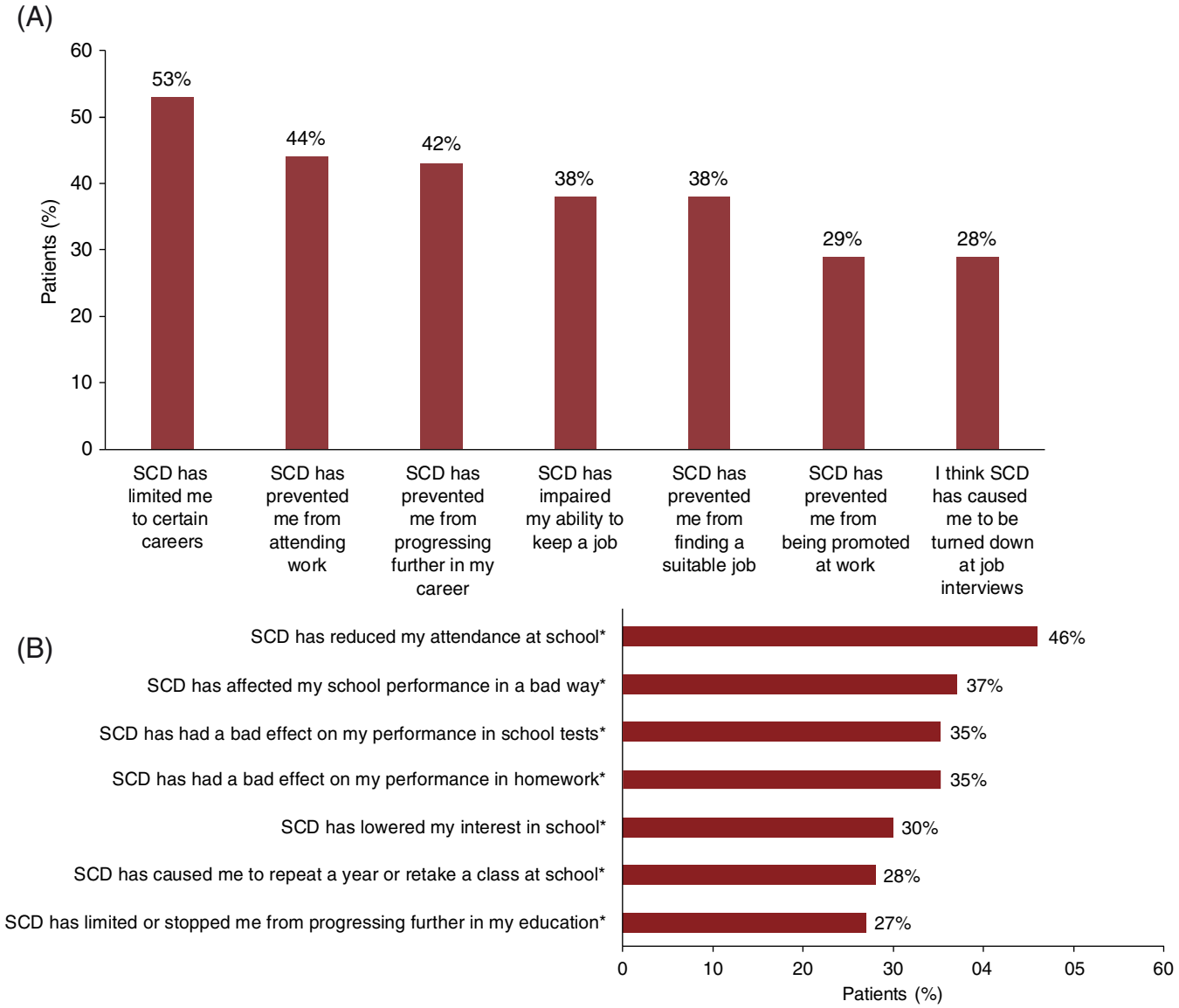

FIGURE 2 Impact of sickle cell disease (SCD) on careers, A (N = 1376) and on schooling, B (N = 769). The percentages show the proportion of patients reporting the effect of their SCD on the statement as high impact (Likert score 5-7). *Patients aged <18 years

that SCD had a high impact (Likert score 5-7) on achievement at school, whereas similar proportions of patients in HI (n = 388/927, 42%) and LMI (n = 176/449, 39%) countries stated that SCD decreased motivation at school. The median age of the 927 patients in HI countries was 32.0 years (IQR 26.0-39.0), compared with 26.0 years (IQR 21.0-33.5) for the 449 patients in LMI countries. Among the 769 patients aged <18 years overall, 46% (n = 356) reported that SCD had reduced their attendance at school; 40% (n = 112/277) in HI countries and 50% (n = 244/492) in LMI countries. In total, 30% (n = 232) of all patients <18 years reported that SCD had reduced their overall interest in school (HI, n = 65 [23%]; LMI, n = 167 [34%]), and 35% (n = 272) reported an adversely affected performance (HI, n = 89 [32%]; LMI, n = 183 [37%]) (Likert score 5-7; Figure 2B).

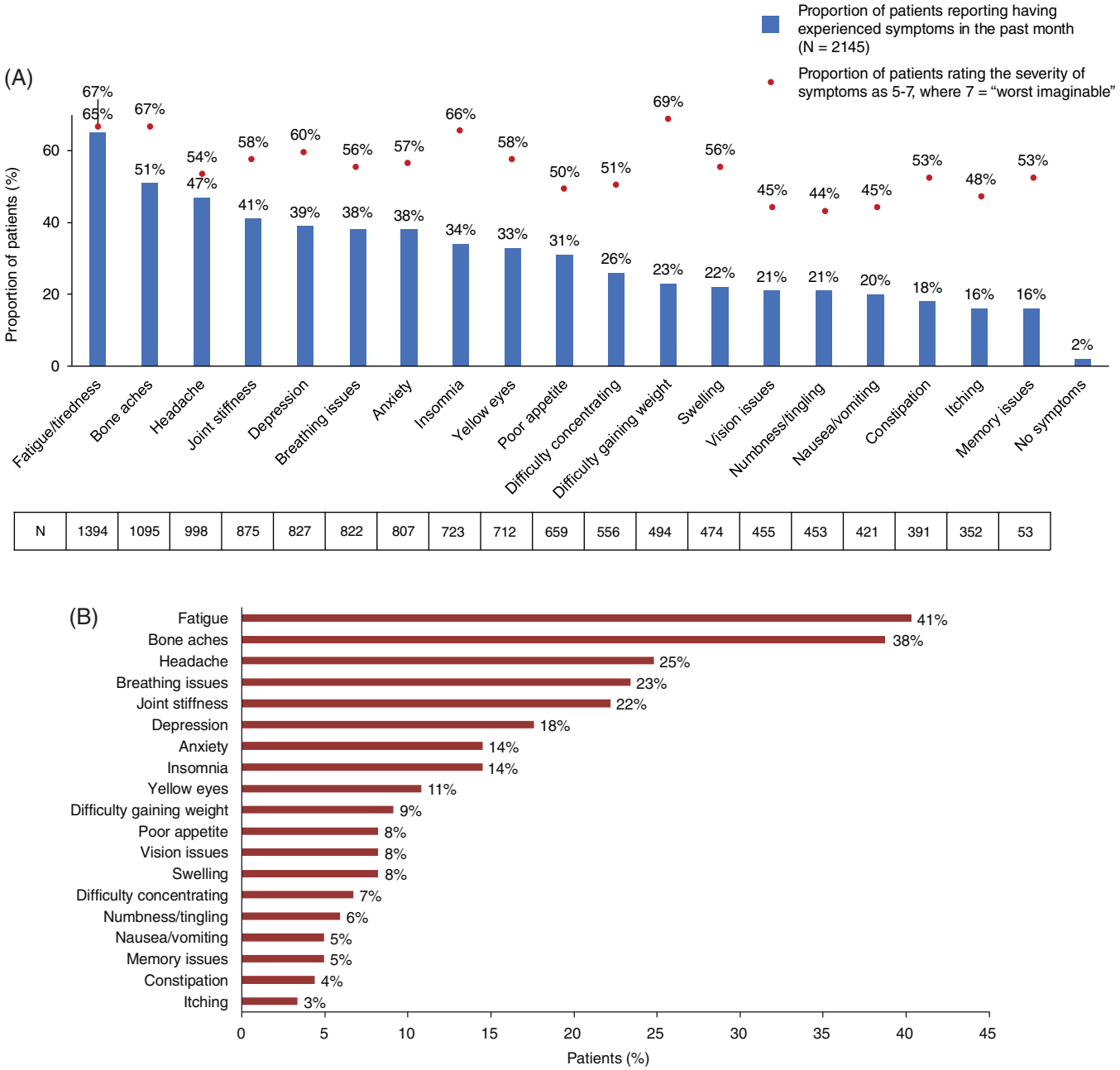

FIGURE 3 A, Most commonly experienced symptoms in the last month and proportion of patients reporting each symptom as "high severity," and, B, the symptoms patients would most like to be resolved (N = 2145). A, Patients ranked symptom severity on a 1-7 Likert scale, where 1 = "not severe at all" and 7 = "worst imaginable." Scores 5-7 indicated "high severity." Vaso-occlusive crises (VOCs) were assessed separately. Patients could select multiple symptoms with no limit on the number selected. B, The percentages show the proportion of patients selecting each symptom as one of the three symptoms they most want to be made better or resolved. VOCs were assessed separately

3.6 | Symptoms reported (excluding vaso-occlusive crises [VOCs])

The three most common symptoms reported among respondents in the month before survey completion (Figure 3A) were fatigue (n = 1394, 65%), bone aches (n = 1095, 51%), and headache (n = 998, 47%). Of those who reported fatigue, 67% rated the symptom severity in the range of "severe" to "worst imaginable" (Likert score 5-7). The severity of bone aches and headache was rated in this range by 67% and 54% of patients, respectively.

Fatigue and bone aches were more frequently reported by patients in HI countries (fatigue, n = 924/1204 [77%]; bone aches, n = 695/1204 [58%]) than by those in LMI countries (fatigue, n = 470/941 [50%]; bone aches, n = 400/941 [43%]). The proportion of patients reporting headache was similar between HI (n = 533/1204, 44%) and LMI countries (n = 465/941, 49%). Of those who reported fatigue, 73% of patients in HI countries and 55% of those in LMI countries rated the symptom severity in the range of "severe" to "worst imaginable" (Likert score 5-7); bone aches was rated as such by 67% of patients in HI countries and by 66% of those in LMI countries, and headache was rated in this range by 58% of patients in HI countries and 51% of patients in LMI countries.

Psychological symptoms were also prevalent, with 39% (n = 827) and 38% (n = 807) of patients reporting depression and anxiety, respectively, in the month before survey completion; these symptoms were reported by 47% (n = 560) and 39% (n = 468) of patients in HI countries and by 28% (n = 267) and 36% (n = 339) of those in LMI countries, respectively. Symptom frequency did not always correspond with symptom severity. For instance, of the 23% (n = 494) of patients in the overall population who reported difficulty gaining weight, 69% rated the symptom as high severity (Figure 3A). Fatigue was the symptom patients most wanted to be resolved, followed by bone aches and headache (Figure 3B). The symptom patients most wanted to be resolved in HI countries was fatigue, followed by bone aches and joint stiffness; in LMI countries, it was bone aches and headache jointly, followed by fatigue. In the 12 months prior to survey completion, background pain was reported on average 2.8 days per week (SD = 2.2), and 3.4 (SD = 2.2) and 2.0 (SD = 1.8) days per week in HI and LMI countries, respectively.

The most common complications are displayed in Figure S4.

3.6.1 | Impact of the top three most common symptoms on daily life, emotional wellbeing, schooling, and employment

Patients who experienced symptoms of fatigue, bone aches, and headache in the month before survey completion were more likely to report that SCD had a high impact on aspects of their daily life, emotional wellbeing, schooling, and employment than those who did not report these symptoms (Table S1). For instance, patients reporting any of these symptoms were significantly more likely to report a high impact of SCD (Likert score 5-7) on their ability to perform daily household activities ($P < .0001$ [MW]), their family or social life ($P < .0001$ [MW]), or their achievement in school ($P < .0001$ [MW]), and that the disease prevented them from progressing further in their chosen career (fatigue, $P < .0001$ [MW]; bone aches, $P < .0001$ [MW]; headache, $P = .0272$ [MW]).

3.7 | VOCs and their management

Patients reported a total of 11 317 VOCs (defined as "severe pain crises" experienced at home, or requiring hospitalization or treatment in an emergency room [ER] or in the community) during the 12 months before survey completion (mean 5.3 [SD = 6.8], median 3.0 [IQR 2.0-6.0] per patient). A median of 4.0 (IQR 2.0-7.0) and 3.0 (IQR 2.0-6.0) VOCs were reported in HI and LMI countries, respectively, in the 12 months prior to survey completion. Almost all patients (n = 1940/2142, 91%) experienced ≥1 VOC in the 12 months before survey completion (Table S2); 91% (n = 1101/1204) in HI countries and 89% (n = 839/938) in LMI countries. In patients aged ≤18 years overall, a median of 3.0 (IQR 2.0-6.0) VOCs were reported. In patients aged >18 years overall, a median of 4.0 (IQR = 2.0-7.0) VOCs were reported.

It was reported that VOCs are most frequently managed by overnight hospitalization in the overall population (33% of VOCs). Other VOCs were managed at home (24%), in the ER (19%), or in the community (24%), which included assistance from a pharmacist, general practitioner, or specialist and included visiting a hospital or healthcare facility but not visits to the ER or overnight hospitalization.

Of 885 patients who indicated why they manage VOCs at home, the most common reason overall was a patient-reported poor experience at the hospital or ER (n = 345, 39%) (Figure S5), followed by thinking that medical assistance was not necessary (n = 263, 30%) and then a belief that HCPs do not understand SCD (n = 230, 26%). Of patients who reported that they managed VOCs at home because they felt that HCPs do not understand SCD (n = 230), 74% reported that the main person responsible for the management of their disease was an SCD specialist. Other primary care providers of patients who managed VOCs at home because they felt that HCPs do not understand SCD were reported as pediatric hematologist (6%); general practitioner/family doctor/general pediatrician (10%); specialist nurse/nurse practitioner (3%); other (eg, ER doctor, traditional healer) (3%); general hospital doctor (ie, not an SCD specialist) (3%); and physician assistant (<1%).

In HI countries, VOCs were reported as being most frequently managed by overnight hospitalization (34%); 28%, 24%, and 15% of VOCs were managed at home, in the community, and in the ER, respectively. In LMI countries, VOCs were reported as being most frequently managed by overnight hospitalization (32%), then in the ER (26%), in the community (25%), and at home (17%). The most common reasons for home management of VOCs in HI countries (n = 607) were a patient-reported poor experience at the hospital or ER (n = 282, 46%), thinking that medical assistance was not necessary (n = 194, 32%), and believing that HCPs do not understand SCD

(n = 183, 30%); in LMI countries (n = 278), the most common reasons for home VOC management were that it is too expensive to go to the hospital for every VOC (n = 102, 37%), thinking that medical assistance was not necessary (n = 69, 25%), that patients feel the pain is too severe to leave the house (n = 63, 23%) and a patient-reported poor experience at the hospital or ER (n = 63, 23%).

The most common VOC management strategies used at home overall (Figure S6; n = 885) were taking fluids (n = 660 [75%]), rest/sleep (n = 654 [74%]), and taking opioid analgesia (n = 509 [58%]).

The most common VOC management strategies at home in HI countries (n = 607) were taking fluids (n = 518, 85%), rest/sleep (n = 507, 84%), and taking opioid analgesia (n = 414, 68%); in LMI countries (n = 278), they were rest/sleep (n = 147, 53%), taking fluids (n = 142, 51%), and use of topical pain medications (n = 127, 46%). 34% (n = 95) of patients in LMI countries managed VOCs at home with opioid analgesia.

3.7.1 | Impact of VOC frequency on daily life, emotional wellbeing, schooling, and employment

Patients reporting a greater number of VOCs in the 12 months before survey completion were significantly more likely to have also reported a high impact of SCD on all aspects of daily life, schooling, and emotional wellbeing assessed in SWAY. Increased VOC frequency was therefore positively correlated with each of these domains (Table S3). Patients reporting more VOCs were more likely to report that SCD had a high impact on the following statements: "SCD interferes with my daily activities" (Spearman's rho, 0.3773; $P < .0001$); "SCD interferes with my family or social life" (Spearman's rho, 0.3575; $P < .0001$); "I feel stressed as a result of my SCD" (Spearman's rho, 0.3515; $P < .0001$); and "SCD has reduced my attendance at school" (Spearman's rho, 0.3813; $P < .0001$). Patients reporting a greater number of VOCs in the 12 months before survey completion were more likely also to have reported a high impact of SCD on some aspects of employment assessed in SWAY (eg, "SCD has impaired my ability to keep a job" [Spearman's rho, 0.3266; $P < .0001$]) but not others (eg, "As a result of my SCD, I have reduced my hours at work" [Spearman's rho, −0.2275; $P < .0001$]) (Table S3).

3.8 | Treatment and management of SCD

Ongoing treatment for SCD was reported by 94% of patients (n = 1995/2123). The full list of treatments patients reported taking at the time of the survey or ever having received are shown in Figure S7. Folic acid was the most common treatment patients were taking at the time of the survey (n = 1248/2123, 59%); reported by 59% (n = 700/1195) of patients in HI countries and 59% (n = 548/928) in LMI countries. Other common treatments patients reported taking at the time of the survey were over-the-counter pain medication (n = 780/2123, 37%), anti-inflammatories (n = 722/2123, 34%), vitamin D (n = 726/2123, 34%), and opioids (n = 719/2123, 34%) (Table S4). Over-the-counter pain medication, anti-inflammatories, vitamin D, and opioids, respectively, were reported by 45% (n = 535/1195), 41% (n = 494/1195), 35% (n = 421/1195), and 50% (n = 601/1195) of patients in HI countries; and by 26% (n = 245/928), 25% (n = 228/928), 33% (n = 305/928), and 13% (n = 118/928) of patients in LMI countries. Table S5 displays the most common treatments patients had previously taken at some point in their treatment history. Thirty-one percent of patients reported taking hydroxyurea (HU) treatment at time of survey (26% [n = 214/818] of patients aged ≤18 years, 34% [n = 438/1304] of adults, 34% [n = 411/1195] of patients in HI countries, and 26% [n = 241/928] of those in LMI countries). In comparison, 42% (n = 900/2145) of patients overall reported having received HU at some point in their treatment history (35% [n = 290/827] of patients aged ≤18 years, 46% [n = 610/1317] of adults, 51% [n = 617/1204] of patients in HI countries, and 30% [n = 283/941] of those in LMI countries). In HI and LMI countries, respectively, 35% (n = 104/301) and 21% (n = 110/517) of patients aged ≤18 years and 34% (n = 307/894) and 32% (n = 131/410) of those aged >18 years were receiving HU at the time of the survey. Table S6 displays the most common surgical procedures undergone by patients.

Overall, 66% of patients scored 5-7 on the Likert scale (indicating that they agreed or strongly agreed with a given statement) when reporting that their treatment effectively managed their symptoms (n = 1393/2123) and controlled their SCD (n = 1394/2123). However, patients had concerns about the short-term (n = 1086/2123 [51%]) and long-term (n = 1283/2123 [60%]) side effects of their treatments. Patients' concerns over specific side effects were not explored in the survey. Of the patients currently taking any pain management medication (n = 1353), 72% would like an alternative medication (Table S7). Most patients (n = 1507/2145 [70%]: HI, n = 853/1204 [71%]; LMI, n = 654/941 [70%]) were confident (score 5-7) in the assessment/treatment they received from their HCP (Figure S8): the majority were managed by an SCD specialist (n = 1296 [60%]: HI, n = 849/1204 [71%]; LMI, n = 447/941 [48%]) (Table S8).

The most commonly selected treatment goal was to improve QoL (n = 1187/2145, 55%); selected by 55% (n = 668/1204) of patients in HI countries and 55% (n = 519/941) in LMI countries. Other common treatment goals were to prevent worsening of SCD (n = 930 [43%]: HI, n = 577 [48%]; LMI, n = 353 [38%]), reduce the number of severe pain crises (n = 638 [30%]: HI, n = 386 [32%]; LMI, n = 252 [27%]), improve overall symptoms (n = 618 [29%]: HI, n = 339 [28%]; LMI, n = 279 [30%]), and improve long-term survival (n = 602 [28%]: HI, n = 338 [28%]; LMI, n = 264 [28%]).

4 | DISCUSSION

SWAY provides real-world data from over 2000 patients with SCD across the globe. To our knowledge it is the largest survey of its type ever conducted and gives unique insights into the impact of SCD on patients' QoL and offers more specificity than previous studies, which may in turn inform the development of individualized disease management strategies by HCPs.

A substantial proportion of the patients surveyed reported that SCD has a high impact on many aspects of their daily lives, including housework, exercise, social life, and relationships. This is consistent with studies evaluating QoL in patients with SCD using standardized HRQoL tests.[10,12,13,15,25] For instance, a generalized impairment in QoL was shown in the PiSCES study (conducted in the USA) and in a study of adolescents with SCD in Africa.[15,26] Similarly, two studies by the Comprehensive Sickle Cell Centers Clinical Trial Consortium demonstrated the diminished QoL of both pediatric and adult patients with SCD across various domains of the SF-36 questionnaire.[12,13] The studies also showed that patients with certain symptoms/complications (eg, vaso-occlusive pain) had lower scores on most HRQoL scales than patients without these symptoms/complications, for both pediatric and adult patients.[12,13] Advancing age and frequent opioid use were associated with lower scores on all HRQoL scales except mental health for adult patients.[12] Preliminary analyses conducted in this study show that patients with greater self-reported VOC and symptom burden appeared to be more likely to report a higher impact of SCD on most aspects of their daily lives, supporting findings from the Comprehensive Sickle Cell Centers Clinical Trial Consortium.

Findings from this survey also illustrated the substantial impact of SCD on patients' working lives, with over half of patients reporting the belief that their income would be higher if they did not have SCD. The SCD symptoms and their effect on a patient's capacity to work, along with a lack of understanding of the disease and its impact on patients by employers, may contribute to this.[27] Increased VOC frequency in the 12 months before survey completion was associated with a higher impact of SCD on some areas of employment but not on others, possibly suggesting that SCD does not universally impact patient employment. The impact of SCD on employment shown here, in addition to the high healthcare utilization associated with SCD, likely results in negative economic consequences for patients, societies, and healthcare systems. SCD is also reported by patients to negatively affect education. An association between poor educational achievement and frequent ER visits has been identified previously, even after controlling for socio-economic factors and independent of disease severity,[28] emphasizing the need to address the negative impact of SCD on education.

Of SCD symptoms (excluding VOCs, which were assessed separately) experienced within the month prior to survey completion, fatigue was reported with the highest frequency. This high patient-reported global prevalence of fatigue supports findings of a recent cross-sectional survey of SCD symptoms in Iran,[29] as well as those from various studies using different HRQoL questionnaires to assess symptom frequency, including the SF-36 questionnaire, Child Health Ratings Inventories, Brief Fatigue Inventory (BFI), Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF), and the Patient-Reported Outcomes Measurement Information System (PROMIS) fatigue short form.[12,13,30,31] For instance, studies using the SF-36 questionnaire report an increased prevalence of fatigue among SCD patients compared with the general population based on poorer scores on the vitality domain in SCD patients. Vitality was defined as "energy level and fatigue."[12,13] Studies evaluating fatigue with the SF-36 questionnaire are limited by only being able to assess the frequency of the symptom. The Comprehensive Sickle Cell Centers Clinical Trial Consortium showed that the presence of various complications such as asthma and sickle cell pain, as well as increasing age, significantly lowered scores in the vitality domain (ie, were associated with increased frequency of fatigue).[12]

Using the BFI questionnaire and the PROMIS Fatigue Short Form (5-point Likert scale assessment), Ameringer et al. 2014 showed that fatigue interfered with SCD patients' mood and daily activities such as schooling and employment.[31] In SWAY, the severity of fatigue is also reported, showing that most patients who experience the symptom consider it to be of high severity. Furthermore, patients with fatigue also had an increased likelihood of reporting a high impact of SCD on all aspects of their daily lives. Resolution of fatigue was selected as the top priority for symptom management, followed by bone aches and headache. Based on these findings, there is an apparent need to include fatigue as an additional marker of overall disease severity in clinical practice, alongside the incidence and severity of VOCs and pain. Severe fatigue in patients should prompt escalation of therapy. Moreover, clinical trials should consider including fatigue as an efficacy endpoint, assessed via validated fatigue scores in SCD such as the MFSI-SF and BFI.[31]

The global prevalence and reported severity of bone aches and headache was similar to that of fatigue in SWAY. This suggests that, in addition to fatigue, bone aches and headache are significant sources of ongoing debilitation from the patient's viewpoint. For some other symptoms reported in SWAY, for example "difficulty gaining weight," the proportion of patients rating the symptom as "high severity" appears unrelated to frequency, indicating that HCPs should specifically enquire about less common symptoms that may have a high impact on patients' daily lives. Further analyses are required to determine whether reported symptoms and symptom severity are affected by patient characteristics, such as gender, age, and country of residence, and to evaluate the impact of various complications on patients' daily lives.

The negative impact of SCD on mental health has been previously identified as contributing to reduced QoL, with country-specific analyses published on this topic.[10,16,17,32] Results from SWAY provide more specific information on the emotional impact of SCD, demonstrating that feelings of stress and helplessness affect patients with SCD across the globe. Just under half of patients reported a strong fear of dying, demonstrating the great emotional burden experienced by many patients with SCD. Addressing this emotional burden is an unmet need, emphasized by the finding that patients would like more professional emotional support.

Findings from SWAY reaffirm results from prior studies showing that VOCs are highly debilitating for patients with SCD,[26,33-36] and expands on these findings by reporting the global burden of these acutely painful events and demonstrating the detrimental impact of VOCs on most aspects of patients' daily lives. The self-reported incidence of VOCs in SWAY appears to be higher than in previous reports,[37,38] although a direct comparison of VOC frequency is limited by differing definitions of a VOC and methodologies[36] for capturing their occurrence. Also, SWAY showed that despite the significant global burden of VOCs, there is still a need to improve management

of VOCs. Almost a quarter of VOCs reported during the 12 months before the time of survey were managed at home, with the main reason given in the overall population being that patients reported a previous poor experience in the ER or hospital, emphasizing the strong need to improve access to expert, equitable, and compassionate care for patients with SCD. Although SWAY did not capture the specific reasons for this, other studies have identified issues with patients feeling stigmatized by some HCPs, who misinterpret requests for strong opioid analgesia as drug-seeking behavior and a sign of addiction, rather than a necessary and appropriate treatment for the severe pain of VOCs.[39-41] This is supported by the SWAY finding that around a quarter of patients managed VOCs at home because they felt that most HCPs do not understand SCD; yet for 75% of those patients, their primary care provider was an SCD specialist.

In terms of SCD treatment, only 42% of patients overall reported that they were either receiving at the time of the survey or had ever received HU, the mainstay drug for the prevention of VOCs. Possible explanations include concerns regarding short- and long-term side effects, lack of knowledge among HCPs,[42,43] and limited availability of HU in some LMI countries.[2] Indeed, fewer patients in LMI countries reported that they were taking HU at the time of the survey or had ever taken the drug than patients in HI countries. Additional treatments beyond those currently utilized are needed to control SCD and improve QoL for more patients.

Several pertinent differences were observed in the reported impact of SCD on daily life between HI and LMI countries. Patients from HI countries consistently reported a higher impact of SCD on their daily life, emotional wellbeing, and employment. There are multiple confounding factors related to geographical location that could account for the differences observed between HI and LMI countries in this analysis. Symptoms such as fatigue were more frequently reported by patients in HI countries than by those in LMI countries, which may reflect the tendency for SCD burden to increase with advancing age, but could equally be due to cultural differences between the two populations; for instance, differing expectations regarding work productivity. More patients in HI than in LMI countries reported that they managed their VOCs at home and that they did so because of poor experience at the ER/hospital. Patients in LMI countries may be less likely to visit the ER/hospital over perceptions of high cost. Economic circumstances may be a prominent contributing factor to the differences between HI and LMI countries in the reasons patients gave for the home management of VOCs, but other factors again cannot be discounted. Considerably more patients in LMI countries reported managing their VOCs at home because they felt that it was too expensive to go to the hospital for every VOC than those in HI countries. Self-reported impact of SCD on aspects of schooling was higher in LMI than HI countries. Differences between HI and LMI countries in educational infrastructure and opportunity could contribute to potential differences in patient-reported impact on schooling. Of note, there were substantially more pediatric patients in the LMI population than in the HI population. Moreover, treatment satisfaction levels and treatment goals were generally similar between HI and LMI countries, indicating a global commonality in unmet treatment needs.

4.1 | Limitations

A considerable strength of the survey is that it captures real-world global data on the overall burden of SCD from the patient viewpoint with greater specificity than studies using standardized HRQoL tests, although the methodology employed here, adapted from prior global disease burden surveys,[18] inherently prevents direct comparisons with such studies and lacks the same validation steps performed for standardized HRQoL tests. Although the use of Likert scales as an outcome measure has been validated in other studies, the potential for one patient to interpret "high impact" differently from another based on their own experiences is a limitation to their use. However, the overall purpose of SWAY was to capture the impact of SCD from the patient's viewpoint, and by including a large patient sample, the data reported here provide an overall representation of patients' reported impact of SCD on their daily lives. Results from SWAY showing that greater VOC and symptom burden was associated with an increased likelihood of patients reporting a high impact of SCD on their daily lives infer the validity of findings in this health burden survey.

As with all patient self-completed surveys, only data from patients willing to participate were captured and, while country-wide recruitment was attempted, patients were mostly recruited from localized specialist centers where large numbers of SCD patients sought care. Since 58% of patients were recruited via HCPs, these patients already seeking subspecialty care may not be fully representative of the general SCD population. The sample was not adjusted if under-recruitment occurred in certain regions.

The average age of patients in LMI countries is much lower than that of the HI group. This may reflect the reduced availability of high-quality care and consequent higher mortality rate in LMI countries. In line with the lower average age of the LMI vs HI population, more patient data in the LMI group were provided by patient proxies, confounding the interpretation of observed differences between the groups. Future analyses of SWAY will explore whether patients' reported impact of SCD on daily life differed between patients completing the survey directly and those who did so by proxy.

In line with the primary aim of SWAY, this manuscript provides a comprehensive overview of the global impact of SCD on various aspects of patients' daily lives. Secondary publications are planned to evaluate patient demographic (eg, country of residence, age, and gender) differences in the impact of SCD on patients' lives and SCD management. As SWAY was not specifically designed to evaluate the potential relationships between the array of variables assessed in the survey, the association between impact of SCD on patients' daily lives and commonly reported symptoms, as well as VOC frequency, should be interpreted with appropriate caution; patients were not asked to consider the impact of individual symptoms, complications, or VOCs on their daily lives but, rather, the impact of SCD overall. In addition, with such a large sample size, and the numerous tests conducted without adjustment for the multiple analysis effect, the findings of statistical significance for individual tests must be treated with caution.

5 | CONCLUSION

The international Sickle Cell World Assessment Survey is the first survey to assess the impact of SCD on patients' daily lives and SCD management, demonstrating the significant impact of SCD on patients' QoL across a large group of diverse countries. In SWAY, it was documented that the priority treatment goal for most respondents was the improvement of QoL. The high burden of VOCs in SCD is well established, and findings from SWAY reaffirm this but expand on the existing literature by demonstrating that other symptoms of SCD, notably fatigue and depression/anxiety, are also highly prevalent and similarly considered of high severity by patients. Healthcare professionals should work closely with their patients to understand how SCD is affecting them personally and, in turn, tailor management strategies according to the individual patient's experience. Also, SWAY shows that while there is a global commonality in unmet treatment needs, self-reported disease burden and impact of SCD on daily life appear to be greater in patients residing in HI countries than in those in LMI countries, potentially owing to a variety of factors related to geographic location (eg, differences in age and economic circumstance between the populations, as well as cultural differences) that are beyond the scope of this analysis. Future analyses of the SWAY database will explore any patient demographic (eg, age, gender, and country of residence) differences in the impact of SCD on patients' lives and SCD management to identify country-specific, region-specific, gender-specific, or age-specific unmet medical needs. Further analyses of SWAY will also fully explore how patient demographic factors (eg, age, gender), VOC and symptom/complication frequency, and treatment use (eg, opioids) influence self-reported impact of SCD on patients' daily lives.

ACKNOWLEDGMENTS

We would like to thank the patients, caregivers, and HCPs who have participated in the SWAY survey, and Adelphi Real World for executing the survey, collating the data, and running the analyses.

We would like to thank Daniel Blumrich (Novartis Pharmaceuticals Corporation) for his substantial contribution to the conceptualization of SWAY, the defining of its objectives and design, and for his role in coordinating the running of the survey.

We would also like to thank Biba Tinga (Sickle Cell Disease Association of Canada), Yolande Adjibi (Fédération SOS Globi), Elvie Ingoli (Interessengemeinschaft Sichelzellkrankheit und Thalassämie), Elmas Citak and Chantelle Rodgers (OSCAR Nederland), Matthew Neal (Sickle Cell Society), and Carolyn Rowley (Cayenne Wellness Center) for their contribution to patient recruitment. We also thank all staff who contributed to patient recruitment from the Italian Association of Pediatric Hematology Oncology, Sickle Cell Disease Association of America, Sickle Cell 101, and Red Moon.

This survey was sponsored by Novartis Pharmaceuticals Corporation. Medical writing assistance was provided by Liz Pearce MBChB, from Mudskipper Business Ltd, funded by Novartis Pharmaceuticals Corporation.

Novartis provided sponsorship and was involved in running the survey. Adelphi Real World (ARW) designed the survey in collaboration with the SWAY steering committee and Novartis. Funding was provided by Novartis Pharmaceuticals Corporation to ARW for the survey design, data collection, and data analysis, and Mudskipper Business Ltd, Bollington, Macclesfield, UK for medical writing support.

CONFLICT OF INTEREST

I.O. reports consultancy for Novartis and Pfizer; speakers' bureau for Novartis, Terumo, and Global Blood Therapeutics; advisory board participation for Novartis, Pfizer, Acceleron, FORMA Therapeutics, and Global Blood Therapeutics; grants from the Health Resources and Services Administration (HRSA), Patient Centered Outcomes Research Institute (PCORI), and Hemedicus (educational); and Data and Safety Monitoring Board (DSMB) membership for Micella Biopharma. B.A. reports consultancy or membership on an advisory committee for bluebird bio, CRISPR/Vertex, Cyclerion, Forma Therapeutics, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi Genzyme, and Terumo BCT; research funding from Imara and Novartis; and DSMB membership for Global Blood Therapeutics. B.P.D.I. reports unrestricted educational funding from Novartis, bluebird bio, AstraZeneca, Vertex, and Global Blood Therapeutics; and steering committee participation for AstraZeneca, Novartis, and Global Blood Therapeutics. F.E.R. reports research funding from Cyclerion, Novartis, and Pfizer; and advisory board participation for Novartis, Global Blood Therapeutics, and bluebird bio. B.F.-G. reports employment by the Sickle Cell Disease Association of America. A.N. reports consultancy/expert testimony for Novartis and bluebird bio. C.P.M. reports consultancy for Novartis, Global Blood Therapeutics, bluebird bio, TauTona, Roche, and Emmaus. C.T. reports consultancy/expert testimony for Novartis, Cyclerion, and Global Blood Therapeutics. M.R.A. reports research funding from Novartis, AstraZeneca, and Modus; honoraria from Novartis, Global Blood Therapeutics, and Novo Nordisk; membership on a board of directors/advisory committee for Global Blood Therapeutics, AstraZeneca, Novo Nordisk, and Crispr Therapeutics; and travel support from Amgen. J.-B.A. reports consultancy/expert testimony and honoraria from Novartis. R.C. reports membership on a board of directors/advisory committee for Novartis, Addmedica, and Global Blood Therapeutics; and consultancy/expert testimony for Novartis. M.dM. reports honoraria and membership on a board of directors/advisory committee for Addmedica, Novartis, bluebird bio, and Vertex. W.J. reports honoraria and consultancy/expert testimony for Novartis. E.N. reports consultancy/expert testimony for Novartis. N.R. is an employee of Novartis Pharma AG. L.D. is an employee of Novartis Pharmaceuticals Corporation. J.J. reports employment by the Sickle Cell Society and honoraria from Novartis. O.R.-H. and T.B. are employees of Adelphi Real World, which received payment from Novartis Pharmaceuticals as part of this research. S.J. and M.P. report no disclosures.

AUTHOR CONTRIBUTIONS

All authors (except Nicholas Ramscar, Laurie DeBonnett, Tom Bailey, and Olivera Rajkovic-Hooley) were members of the SWAY steering

committee, of which Ifeyinwa (Ify) Osunkwo and John James were co-chairs. All authors contributed to the survey design and data interpretation, and reviewed and approved the report. John James, Erfan Nur, Beverley Francis-Gibson, Cassandra Trimnell, Jean-Benoît Arlet, Raffaella Colombatti, Marimilia Pita, and Suman Jain contributed to patient recruitment.

DATA AVAILABILITY STATEMENT

Novartis is committed to sharing with qualified external researchers access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations.

This trial data availability is according to the criteria and process described on www.clinicalstudydatarequest.com

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Osunkwo I, Andemariam B, Minniti CP, et al. Impact of sickle cell disease on patients' daily lives, symptoms reported, and disease management strategies: Results from the international Sickle Cell World Assessment Survey (SWAY). *Am J Hematol*. 2021;96:404–417. https://doi.org/10.1002/ajh.26063