



Illness Intrusiveness in Adults with Sickle Cell Disease: The Role of Fatigue

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Abstract

Chronic illness experiences often interfere with daily functioning (a concept known as illness intrusiveness) and health-related quality of life (HRQoL). However, less is known about the role of specific symptoms in predicting illness intrusiveness in sickle cell disease (SCD). This exploratory study examined associations between common SCD-related symptoms (i.e., pain, fatigue, depression, and anxiety), illness intrusiveness, and HRQoL among adults with SCD ($n=60$). Illness intrusiveness significantly correlated with fatigue severity ($r=.39$, $p=.002$), depression severity ($r=.45$, $p<.001$), anxiety severity ($r=.41$, $p=.001$), physical HRQoL ($r=-.53$, $p<.001$), and mental HRQoL ($r=-.44$, $p<.001$). Multiple regression revealed a significant overall model, ($R^2=.28$, $F(4, 55)=5.21$, $p=.001$), with fatigue, but not pain, depression, or anxiety, significantly predicting illness intrusiveness ($\beta=.29$, $p=.036$). Results suggest that fatigue may be a primary factor contributing to illness intrusiveness—a determinant of HRQoL—in individuals with SCD. Given the limited sample size, larger confirmatory studies are warranted.

Keywords Sickle cell disease · Quality of life · Pain · Fatigue · Depression

Introduction

Sickle cell disease (SCD) is a group of genetic blood disorders that affects approximately 100,000 individuals in the United States (Hassell, 2010). Individuals with SCD have a genetic mutation that alters hemoglobin, a protein found in red blood cells, resulting in sickle-shaped red blood cells that obstruct blood vessels and inhibit the flow of oxygen and vital nutrients throughout the body. Consequently, SCD affects multiple organ systems, and people with SCD are at risk for increased morbidity and mortality relative to the general population (Kato et al., 2018; Lubeck et al., 2019; Payne et al., 2020; Platt et al., 1994). Pain and fatigue are

two of the most common SCD symptoms (Ahmadi et al., 2018; Ameringer et al., 2014; Osunkwo et al., 2021; Smith et al., 2008). Individuals with SCD experience intermittent severe pain episodes and chronic pain (Smith et al., 2008). Studies show that adults with SCD report pain at least 50% of the days within a six-month period, and 30% report daily pain. Less research has focused on fatigue; however, recent work suggests that about 65% of individuals report experiencing fatigue (Ahmadi et al., 2018), with average levels in the moderate range (Ameringer et al., 2014). Depressive and anxiety symptoms are also common co-occurring issues, with estimates of about 18% to 28% for depressive symptoms and 6.5% to 25% for anxiety symptoms (Jonassaint et al., 2022; Levenson et al., 2008; Oudin Doglioni et al., 2021; Robbins et al., 2020).

In the context of multiple symptoms and health complications, adults living with SCD report lower health-related quality of life (HRQoL) than the general population (Freitas et al., 2018; Treadwell et al., 2014). HRQoL refers to people's appraisal of their well-being and functioning relative to their ideals and expectations (Centers for Disease Control & Prevention, 2001; Megari, 2013). HRQoL is a multidimensional construct consisting of physical, mental, and social domains that are affected by disease and treatment factors

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(Megari, 2013). It is an essential construct to evaluate in people living with a chronic health condition because it goes beyond measuring the presence or severity of a disease to assess an individual's happiness and life satisfaction. Assessing HRQoL is a widely used approach that increases awareness about the impact of chronic health conditions, which can help guide interventions and the allocation of resources.

The concept of illness intrusiveness is an important determinant of well-being and HRQoL in adults with chronic health conditions (Devins, 2010). Illness intrusiveness is defined as the extent to which features of a disease and associated treatment factors interfere with an individual's ability to participate in valued daily activities (Devins et al., 1983). Devins' illness intrusiveness theoretical framework proposes that a combination of disease and treatment factors indirectly compromises HRQoL and contributes to emotional distress by disrupting participation in lifestyles, interests, and meaningful activities. The nature and impact of chronic health conditions are heterogeneous. Therefore, illness intrusiveness is a critical concept to examine because it illustrates the impact of the disease experience on a particular person or population. Illness intrusiveness is also a modifiable risk factor for, rather than a downstream effect of, HRQoL.

Illness intrusiveness and its association with HRQoL have been well-studied in several chronic health conditions, such as cancer, end-stage renal disease, and multiple sclerosis (Bloom et al., 1998; Devins, 1994, 2010; Edelstein et al., 2016; Shawaryn et al., 2002). Greater illness intrusiveness is strongly and consistently associated with lower HRQoL. Pain and fatigue are two commonly cited physical correlates of illness intrusiveness; higher levels of pain and fatigue are associated with greater illness intrusiveness (Bouchard et al., 2017; Goudsmit et al., 2009; Gromisch et al., 2019; Novak et al., 2010; Simoncsics et al., 2022). Depression and anxiety are psychological correlates of illness intrusiveness; higher levels of depressive and anxiety symptoms are associated with greater illness intrusiveness (Altaras et al., 2022; Gromisch et al., 2019; Simoncsics et al., 2022; Snyder et al., 2013; Thakur et al., 2018).

Lower HRQoL in adults with SCD may be due to intrusions it presents in daily activities, and these intrusions may help explain the link between SCD-related symptoms and HRQoL. Pain is the hallmark symptom of the condition, and more severe pain is associated with lower physical and mental HRQoL in adults with SCD (Anie et al., 2002; Ballas et al., 2006; Freitas et al., 2018). Greater pain frequency is also associated with reduced engagement in social activities (Gil et al., 1992), and higher daily pain severity ratings are associated with reduced same-day work attendance (Gil et al., 2004). Although pain has received the most attention in the literature, researchers have begun to examine fatigue and its relationship with HRQoL. Greater fatigue is moderately to strongly associated with physical and mental

HRQoL (Ameringer et al., 2014). In a recent large-scale international study, fatigue was the most reported non-pain symptom (Osunkwo et al., 2021). Individuals who reported fatigue were more likely to report that SCD highly impacted their daily life, household activities, family or social life, employment, and emotional well-being. Depressive and anxiety symptoms—other correlates of HRQoL in SCD—were also prevalent (Osunkwo et al., 2021). Little is known about the intrusiveness of psychological symptoms in SCD. However, research in other populations suggests that depressive and anxiety symptoms may contribute to greater illness intrusiveness. Indeed, more depressive and anxiety symptoms are associated with greater illness intrusiveness in chronic health conditions, including multiple sclerosis and low back pain (Altaras et al., 2022; Gromisch et al., 2019; Simoncsics et al., 2022; Snyder et al., 2013).

Despite evidence that living with SCD is associated with physical and psychological symptoms that may disrupt life activities, no studies have explicitly examined the illness intrusiveness theoretical framework—especially factors that contribute to illness intrusiveness—in this population. Thus, treatments have historically focused on treating symptoms rather than gaining a greater understanding of the relationships between symptoms, illness intrusiveness, and HRQoL. Identifying which symptoms are most related to illness intrusiveness may support the development of more targeted interventions to improve HRQoL.

The objective of this exploratory study was to examine illness intrusiveness and its relationship with pain, fatigue, depressive symptoms, anxiety symptoms, and HRQoL in a sample of adults living with SCD. We examined whether: (1) physical (i.e., pain, fatigue) and psychological (i.e., depressive and anxiety symptoms) factors would be associated with illness intrusiveness and (2) illness intrusiveness would be associated with physical and mental HRQoL. We proposed the latter aim to replicate prior findings of the association between illness intrusiveness and HRQoL, thereby justifying the primary aim of exploring potential risk factors for illness intrusiveness. We hypothesized that greater illness intrusiveness would be associated with higher levels of pain, fatigue, depressive symptoms, and anxiety symptoms and lower physical and mental HRQoL.

Methods

Participants

The study sample consisted of 60 adults with SCD recruited from community organizations and academic medical centers across the United States. Staff at the sickle cell clinics and community organizations posted and electronically distributed the study flyer to patient and community lists.

Participants were recruited from October 2018 to April 2019. Individuals were eligible to participate in the study if they were at least 18 years old, could read and write in English, had access to an internet-enabled device, and were diagnosed with a SCD genotype.

Procedures

This was a cross-sectional survey-based study. Diagnostic status was confirmed by asking potential participants to provide: (1) the name of their SCD provider; (2) the name and location of their SCD treatment facility; and (3) a copy of a medical document with SCD listed as a diagnosis. After verification, they received a link to complete the informed consent process and survey online. Protected health information, including medical record information, was removed from the study record after verification of diagnosis to promote confidentiality of responses. Informed consent was obtained in accordance with procedures approved by the University of Maryland, Baltimore County's institutional review board. After completing the survey, participants received a \$20 Amazon gift card.

Measures

The online survey assessed demographic variables, pain severity, fatigue severity, ED visits, depressive symptoms, anxiety symptoms, and illness intrusiveness, and HRQoL.

Emergency Department Visits

Participants reported the number of times they visited the emergency department for a SCD-related problem in the past 12 months. Previous research has shown that 12-month recall of ED visits is accurate in this population (Haywood et al., 2014; McCrae & Lumley, 1998).

Pain Severity

The Pain Severity Subscale of the Brief Pain Inventory – Short Form (BPI) is a 4-item, self-administered questionnaire that assesses four dimensions of pain: current, worst, least, and average pain in the last 24 h (Cleeland & Ryan, 1994). Participants rate their level of pain using a Likert scale ranging from 0 (*no pain*) to 10 (*pain as bad as you can imagine*). Overall pain severity is calculated by averaging the four scores. Scores range from 0 to 10, with higher scores indicating more severe pain. In this study, the BPI demonstrated excellent internal consistency ($\alpha=0.90$).

Fatigue Severity

The Fatigue Severity Subscale of the Brief Fatigue Inventory (BFI) is a 3-item, self-administered questionnaire that assesses three dimensions of fatigue: current, worst, and average fatigue in the last 24 h (Mendoza et al., 1999). Participants rate their level of fatigue using a Likert scale ranging from 0 (*no fatigue*) to 10 (*as bad as you can imagine*). Overall fatigue severity is calculated by averaging the three scores. Scores range from 0 to 10, with higher scores indicating more severe fatigue. The BFI demonstrated excellent internal consistency ($\alpha=0.95$) in the present sample.

Depressive symptoms

The Patient Health Questionnaire (PHQ-9) is a 9-item, self-report questionnaire that measures depressive symptoms, including (1) anhedonia, (2) depressed mood; (3) insomnia or hypersomnia; (4) fatigue; (5) poor appetite or overeating; (6) feelings of worthlessness; (7) trouble concentrating; (8) psychomotor changes; and (9) suicidal ideation (Kroenke et al., 2001). Participants rate the extent to which they have been bothered by the problems over the last two weeks, using a 4-point Likert scale ranging from 0 (*not at all*) to 3 (*nearly every day*). A sum score is calculated, with higher scores representing more severe depressive symptoms. The PHQ-9 demonstrated good internal consistency ($\alpha=0.86$) in this sample.

Anxiety symptoms

The Generalized Anxiety Disorder-7 Scale (GAD-7) is a 7-item, self-report questionnaire that measures anxiety symptoms, including (1) feeling nervous, anxious, or on edge (2) difficulty controlling worry; (3) excessive worry; (4) trouble relaxing; (5) restlessness; (6) irritability; and (7) feeling afraid as if something awful might happen (Spitzer et al., 2006). Participants rate the extent to which they have been bothered by the problems over the last two weeks. Using a 4-point Likert scale ranging from 0 (*not at all*) to 3 (*nearly every day*). A sum score is calculated, with higher scores indicating more severe anxiety symptoms. Cut points of 5, 10, 15 indicate mild, moderate, and severe symptoms of anxiety, respectively. The GAD-7 demonstrated good internal consistency ($\alpha=0.90$) in this sample.

Illness Intrusiveness

The Illness Intrusiveness Rating Scale (IIRS) is a 13-item, self-report questionnaire that measures illness-induced disruptions in 13 life domains: health, diet, work, active recreation, passive recreation, financial situation, relationship with partner, sex life, family relations, other social relations,

self-improvement/self-expression, religious expression, and community/civic involvements (Devins et al., 1983; Lorig et al., 2001). Using a seven-point scale ranging from 1 (*not very much*) to 7 (*very much*), participants rate the degree to which their illness or its treatment interfere with these life domains (Lorig et al., 2001). This measure yields a composite score, ranging from 13 to 91, based on the sum of the 13 items. Higher scores indicate more illness intrusiveness. During data collection, two items of the family relations domain of the IIRS were inadvertently omitted; thus, data reflect 11 of the 13 items, and family relations was reflected in a single item (“How does sickle cell disease and/or its treatment interfere with your relationship with your spouse or domestic partner?”) The 11-item version yielded a composite score, ranging from 11 to 77. The 11-item version demonstrated good internal consistency ($\alpha=0.88$) consistent with the full version used in prior studies.

Health-Related Quality of Life

The Short Form-12 Health Survey 1.0 (SF-12) is a 12-item, self-report questionnaire that measures two broad categories of HRQoL: physical health and mental health (Ware et al., 2001). Example items include: “During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?” and “During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?” Scores for the SF-12 physical and mental composite scores range from 0 to 100, with higher scores indicating better HRQoL. The SF-12 physical ($\alpha=0.84$) and mental ($\alpha=0.75$) demonstrated adequate internal reliability.

Data Analyses

We examined the data for recording accuracy, missing values, and violations of normality, linearity, and homoscedasticity. We had complete data for the primary study variables for all participants. Scores for the PHQ-9 and GAD-7 were skewed (2.07), and the PHQ-9 was kurtotic (4.81) due to outliers. Analyses were repeated with and without outliers, with consistent results. Analyses were performed in SPSS version 28.0.

Means, standard deviations, and frequencies were calculated for descriptive analyses. A preliminary series of Pearson’s correlations, point-biserial correlations, and one-way ANOVAs were performed to identify potentially relevant demographic and clinical covariates (i.e., age, sex, employment status, genotype, hydroxyurea use, healthcare utilization assessed via emergency department visits, level of education, and marital status) to include in regression

analyses. None of these variables emerged as significantly associated with illness intrusiveness at the 0.05 alpha level; therefore, they were not included in subsequent analyses. Pearson correlations were performed to examine the individual associations between illness intrusiveness, each of the four SCD symptoms of interest (i.e., pain, fatigue, depressive symptoms, anxiety symptoms), and HRQoL. We also conducted an exploratory multiple linear regression analysis examining the four SCD-related symptoms as predictors of illness intrusiveness.

We conducted a post-hoc power analysis for correlation and multiple linear regression using G*Power version 3.1.9.4 (Faul et al., 2007, 2009). Correlation coefficients ranged from 0.21 for pain severity to 0.53 for physical HRQoL. Given $r=0.21$, $\alpha=0.05$, and a sample size of 60, statistical power $(1-\beta)=0.21$. Given $r=0.53$, $\alpha=0.05$, and a sample size of 60, statistical power $(1-\beta)=0.99$. Since power was greater than 0.80, we had adequate power to detect a significant association between illness intrusiveness and all primary variables, except pain severity. As for multiple linear regression, with $f^2=0.38$, $\alpha=0.05$, 4 predictors, and a sample size of 60, statistical power $(1-\beta)=0.97$. We had adequate power to detect a significant effect for the full multiple linear regression model. Effect sizes for individual predictors in multiple linear regression ranged from $f^2=0$ for pain severity to $f^2=0.04$ for fatigue severity. Given $f^2=0$, $\alpha=0.05$, 1 predictor, and a sample size of 60, statistical power $(1-\beta)=0$. Given $f^2=0.04$, $\alpha=0.05$, 1 predictor, and a sample size of 60, statistical power $(1-\beta)=0.33$. We potentially did not have adequate power to detect significant effects for individual predictors in the multiple linear regression model.

Results

All participants identified as non-Hispanic, Black (94.9%) or Biracial (5.1%), with those identifying as Biracial indicating Black to be a part of their racial identity. Participants were predominantly female (69.5%), and their ages ranged from 18 to 69 ($M=39.1$, $SD=12.6$ years). Approximately 76% of the participants were single or previously partnered (e.g., divorced, widowed). The sample was highly educated, with 30.5% completing some college and 57.7% having a bachelor’s or advanced degree. Twenty-five participants (42.4%) were unemployed. Thirty-eight (64.4%) participants were diagnosed with genotypes associated with more clinical severity (i.e., HbSS or HbS β^0). About 44% of participants were prescribed hydroxyurea, a medication that increases fetal hemoglobin and decreases the frequency of pain episodes in individuals with SCD. Descriptive statistics for the primary study variables are presented in Table 1.

Table 1 Descriptive statistics for primary study variables (N=60)

| Variable | M (SD) | Minimum | Maximum |
|-----------------------|---------------|---------|---------|
| Pain severity | 3.29 (2.33) | 0 | 9.00 |
| Fatigue severity | 5.32 (2.74) | 0 | 10.00 |
| Depressive symptoms | 7.50 (5.36) | 0 | 25.00 |
| Anxiety symptoms | 5.48 (5.30) | 0 | 20.00 |
| Illness intrusiveness | 41.72 (15.14) | 11.00 | 72.00 |
| Physical HRQoL | 38.08 (11.21) | 18.17 | 59.38 |
| Mental HRQoL | 44.01 (9.97) | 17.90 | 60.90 |

HRQoL Health-related quality of life

Correlations between SCD symptoms of interest, illness intrusiveness, and HRQoL are presented in Table 2. Consistent with our first hypothesis, participants who reported higher levels of illness intrusiveness had significantly greater fatigue ($r=0.39, p=0.002$), depressive symptoms ($r=0.45, p<0.001$), and anxiety symptoms ($r=0.41, p=0.001$); however, illness intrusiveness was not correlated with pain severity ($r=0.15, p=0.257$). Consistent with our second hypothesis, greater illness intrusiveness was significantly associated with lower physical ($r=-0.53, p<0.001$) and mental ($r=-0.44, p<0.001$) HRQoL. Table 3 presents the multiple linear regression results. The overall regression model was statistically significant ($R^2=0.28, F(4, 55)=5.21, p=0.001$), accounting for 28% of the variance of illness intrusiveness. Fatigue severity significantly predicted illness intrusiveness ($\beta=0.29, SE=0.75, t=2.15, p=0.036$). Pain severity ($\beta=0.000, SE=0.82, t=0.001, p=0.999$), depressive symptoms ($\beta=0.17, SE=0.63, t=0.79, p=0.452$), and anxiety symptoms ($\beta=0.21, SE=0.61, t=1.01, p=0.319$) did not significantly predict illness intrusiveness.

Discussion

The present study evaluated tenets of the illness intrusiveness theoretical framework in individuals with SCD, specifically examining the relationships between SCD-related

Table 3 Multiple linear regression model for predictors of illness intrusiveness

| Variable | b | SE b | β | t | p |
|---------------------|-------|------|---------|------|-------|
| Constant | 26.32 | 4.19 | | 6.29 | <.001 |
| Pain severity | .001 | .82 | .000 | .001 | .999 |
| Fatigue severity | 1.60 | .75 | .29 | 2.15 | .036 |
| Depressive symptoms | .48 | .63 | .17 | .76 | .452 |
| Anxiety symptoms | .61 | .61 | .21 | 1.01 | .408 |

$R^2=.28, F(4, 55)=5.21, p=.001$

symptoms (pain, fatigue, depressive symptoms, anxiety symptoms), illness intrusiveness, and HRQoL. Fatigue was common and, on average, moderate in severity. Pain was also frequently reported but less common and less severe than fatigue. Participants reported moderately severe depressive and anxiety symptoms. Participants also reported moderate levels of illness intrusiveness and HRQoL.

Fatigue severity emerged as a significant predictor of illness intrusiveness in bivariate and multivariate analyses controlling for other SCD symptoms. Other symptoms, including depression and anxiety, were also positively associated with illness intrusiveness but were no longer significant when included in the model with fatigue. Illness intrusiveness was negatively associated with physical and mental HRQoL. Pain was not associated with illness intrusiveness in bivariate or multivariate analyses. These results partially support previous studies showing that illness intrusiveness is linked to disease factors and HRQoL. This study expands our knowledge by showing that the tenets of the illness intrusiveness theoretical framework may be applicable in SCD: adults perceive SCD-related symptoms, particularly fatigue, as intrusive and contributing to diminished HRQoL.

As hypothesized, individuals who reported more severe symptoms of fatigue, depression, and anxiety experienced more illness intrusiveness. However, fatigue emerged as the only significant factor when accounting for all the SCD-related symptoms. Several biological (e.g., anemia, vaso-occlusion) and behavioral (e.g., stress, poor sleep) factors

Table 2 Correlations between primary study variables

| | 1 | 2 | 3 | 4 | 5 | 6 |
|--------------------------|---------|---------|---------|---------|---------|------|
| 1. Pain severity | | | | | | |
| 2. Fatigue severity | .41** | | | | | |
| 3. Depressive symptoms | .13 | .35** | | | | |
| 4. Anxiety symptoms | .03 | .19 | .83*** | | | |
| 5. Illness Intrusiveness | .31 | .39** | .45*** | .41** | | |
| 6. Physical HRQoL | -.59*** | -.45*** | -.02 | .08 | -.53*** | |
| 7. Mental HRQoL | -.04 | -.22 | -.72*** | -.71*** | -.44*** | -.09 |

HRQoL Health-related quality of life

* $p<.05$ ** $p<.01$ *** $p<.001$

likely contribute to fatigue and its negative impact in SCD (Ameringer & Smith, 2011). Fatigue, however, is also a symptom of major depressive disorder and generalized anxiety disorder (American Psychiatric Association, 2013). Results of this study suggest that fatigue may be the driving factor in the relationships between depressive/anxiety symptoms, illness intrusiveness, and HRQoL. However, additional research is needed to examine the nature and temporal relationships between these factors (i.e., moderation and mediation analyses). Furthermore, it is often difficult to determine fatigue etiology in research and practice with complex conditions like SCD. SCD patients may withdraw from important life domains in the presence of fatigue, given the potential uncertainty of the cause and limited information about managing fatigue. In contrast, they may continue to engage in activities when experiencing mild to moderate pain or other common symptoms.

The significant association between illness intrusiveness and fatigue, depressive, and anxiety symptom severity is consistent with previous studies. Conversely, our finding that pain is not significantly associated with illness intrusiveness is generally inconsistent with previous work. However, the results of our study are difficult to compare to others, given the difference in study procedures, measures, analyses, and variables of interest. For instance, few studies have evaluated pain, fatigue, depression, anxiety, and illness intrusiveness in the same sample. In a study of adults with myalgic encephalomyelitis, fatigue and depressive symptoms were positively associated with illness intrusiveness; however, the authors did not assess pain and anxiety symptoms (Goudsmit et al., 2009). The authors also did not conduct multiple regression to evaluate the relative contributions of the various disease-related factors, limiting our understanding of symptoms that may be most intrusive.

In other studies, the authors evaluated pain (and often depressive symptoms) but not fatigue or anxiety (Gromisch et al., 2019; Novak et al., 2010; Simoncsics et al., 2022). Pain severity was positively associated with illness intrusiveness in adults with multiple sclerosis, even after adjusting for disability status (Gromisch et al., 2019). In a prospective study, pain severity at baseline predicted illness intrusiveness at 2- to 3- month follow-up, adjusting for age, sex, education, and pain acceptance in adults with low back pain (Simoncsics et al., 2022). However, pain severity was not a significant predictor of illness intrusiveness after including depression in the model. In the full model, depressive symptoms and pain acceptance were the only significant predictors of illness intrusiveness. In another sample of adults with multiple sclerosis, pain, fatigue, and depressive symptoms—but not anxiety symptoms—were evaluated in relation to illness intrusiveness (Bouchard et al., 2017). Correlation analyses revealed that participants who reported more severe pain, fatigue, and depressive symptoms experienced

greater illness intrusiveness. Path analysis demonstrated that fatigue and depressive symptoms were directly associated with illness intrusiveness, but pain was not. Instead, pain predicted fatigue, which predicted depressive symptoms. Then, depressive symptoms predicted illness intrusiveness. As previously noted, these results suggest potential direct and indirect relationships between fatigue, pain, and depressive symptoms, which should be further explored in future research. Furthermore, there may be unique aspects of fatigue that are distinct from other symptoms in individuals with SCD.

Few studies have examined anxiety in the context of the illness intrusiveness theoretical framework. Among the few, most have examined anxiety and depressive symptoms but not pain, fatigue, or other physical symptoms. Researchers have found that individuals with multiple sclerosis who report more severe anxiety and depressive symptoms experience greater illness intrusiveness; however, these studies did not examine the relative contribution of the symptoms compared to each other (Altaras et al., 2022; Snyder et al., 2013). Anxiety was positively correlated with illness intrusiveness in a sample of adults with chronic obstructive pulmonary disease (COPD) (Thakur et al., 2018). However, there was no significant correlation after adjusting for depressive symptoms and coping factors. More research should examine anxiety and its impact on illness intrusiveness.

Consistent with the literature, illness intrusiveness was negatively associated with physical and mental HRQoL. In adults with myalgic encephalomyelitis and multiple sclerosis, individuals experiencing greater illness intrusiveness reported lower physical functioning (Bouchard et al., 2017; Goudsmit et al., 2009). These studies did not assess mental HRQoL. Another study of individuals with multiple sclerosis demonstrated that illness intrusiveness is also associated with mental HRQoL (Shawaryn et al., 2002). However, mental HRQoL needs further evaluation within the illness intrusiveness theoretical framework.

Implications

The current findings have important theoretical and research implications. Researchers should consider using the illness intrusiveness theoretical framework to better understand the impact of the SCD experience on HRQoL. In addition to accessing specific SCD symptoms, researchers should evaluate disruptions in life activities caused by disease-related factors. Examining multiple disease-related symptoms and complications may be particularly insightful rather than examining the impact of a single symptom, which is often the case in studies examining pain interference. This approach may help researchers identify symptoms contributing the most to illness intrusiveness and HRQoL. The results also highlight that fatigue is an important, under-assessed

SCD-related symptom that warrants further research and clinical focus.

Psychologists in medical settings may consider several clinical implications of this study. The findings highlight the importance of assessing psychosocial factors in adults with SCD presenting with fatigue. Fatigue is likely influenced by several biobehavioral factors, including anemia, pain episodes, and poor sleep, and is also a symptom of psychological disorders such as depression and anxiety. Therefore, healthcare providers should conduct a thorough assessment of fatigue to determine the most probable cause(s) of fatigue and tailor evidence-based behavioral interventions toward the purported cause(s). Partnering with medical team members to treat anemia or other medical conditions in conjunction with psychosocial factors contributing to fatigue promotes patient-centered and comprehensive care. For SCD patients who also endorse symptoms of depression or anxiety, referral for further assessment and intervention with a psychologist is indicated. Psychologists with expertise in health and rehabilitation psychology who work in medical settings and have training in behavioral interventions for managing pain and fatigue related to physical health conditions may be particularly helpful. However, we also acknowledge that at present, there are no validated cutoffs for fatigue in terms of impact on illness intrusiveness. Future work is needed to determine useful clinical cutoffs.

The present study also highlights interactions between the person and the environment when managing chronic health conditions like SCD. Fatigue is amendable to cognitive behavioral interventions; therefore, efforts that target cognitive appraisals [e.g., cognitive behavioral therapy; (Beck, 2011)] and encourage individuals to engage in valued activities [e.g., behavioral activation; (Jacobson et al., 1996); acceptance and commitment therapy; (Hayes et al., 2012)] may have utility and potential efficacy for reducing illness intrusiveness, and ultimately improving HRQoL in this population.

Limitations

Several limitations should be considered. This exploratory study had a small sample size, which decreased the statistical power to perform more advanced multivariate and mediational analyses ideal for comprehensively validating theoretical models. Although participants were recruited from multiple sites across the country, the findings of this study have limited generalizability because the sample mostly consisted of females (i.e., 70% identified as female) and was highly educated (i.e., 88% completed at least some college and 58% earned a bachelor's or advanced degree). Larger-scale studies with community-based recruitment partnerships will be needed to ensure adequate power for future samples and representation of the SCD community.

There were some issues during the data collection phase. Initially, participants were recruited from a single adult sickle cell clinic in the mid-Atlantic. To improve recruitment efforts, we expanded the scope of recruitment to sickle cell clinics and sickle cell organizations across the United States. The survey link was publicly available, and unfortunately, there were many invalid responses. Due to concern about the invalid responses, we revised the study procedures to include a quality check in which individuals confirmed their SCD diagnosis before gaining access to the study survey. It is recommended that future research directly recruit and enroll individuals from multiple sickle cell clinics.

In the current study, two of the three items from the family relations subscale of the illness intrusiveness measure were inadvertently omitted from administration. Although we did not fully capture this subdomain, the global construct was likely still captured. Including the two items would likely have resulted in similar or higher scores on the IIRS, and a potentially stronger association between illness intrusiveness and disease factors and HRQoL. Additionally, the IIRS has not previously been validated in adults with SCD; however, it has been used in individuals with other chronic health conditions, including ones characterized by pain. A larger-scale study is needed to validate the IIRS in adults with SCD.

Given the cross-sectional study design, the causal relationship or the temporal ordering could not be established. There was also a difference in timing among the variables. For example, HRQoL was assessed over the past month, and pain and fatigue were assessed over the past 24 h. Future research using the illness intrusiveness theoretical framework should conduct experimental studies to evaluate the temporal ordering of the variables and make inferences about causality being mindful of the timeframe used for each instrument. Future studies should also utilize path analysis to examine the goodness of fit for the full model proposed within the illness intrusiveness theoretical framework, as most previous research, including the present study, has only evaluated parts of the framework. Lastly, it was assumed that the 13 life domains assessed by the IIRS are valuable or meaningful for individuals. While the 13 life domains are often important for individuals, this is not necessarily true for all individuals with a specific chronic health condition. In this study, participants were given the option to indicate if a domain was “not applicable” for them, which is possibly a way for them to express that a domain is not important to them. Eight participants indicated that at least one item was “not applicable.” These items were scored as 1, as suggested by (Lorig et al., 2001). Mixed methods and qualitative research in this area may help characterize the importance and relevance of these domains. Inclusion of the importance subscale of the Disability Centrality Scale

may also be a useful supplemental measure (Bishop et al., 2008). Furthermore, further refinement of measures in the model that are specific to SCD (e.g., ASCQ-Me) and provide more nuanced assessment of complex symptoms (e.g., pain) is warranted in future research.

Strengths

Despite these limitations, there were also strengths. This study was grounded in Devin's illness intrusiveness theoretical framework, which has been well-studied and supported in other chronic health conditions. In addition to pain, the most studied SCD symptom, we concurrently examined the impact of fatigue, depressive, and anxiety symptoms. This approach helped illuminate the intrusive nature of fatigue relative to pain and other SCD-related symptoms. Our inclusion of depressive and anxiety symptoms also demonstrated the importance of considering psychological symptoms in this population. Although the IIRS has not been validated in adults with SCD, it demonstrated good internal consistency in this sample. Illness intrusiveness examines domains similar to pain and fatigue interference; however, illness intrusiveness (particularly as assessed by the IIRS) considers the impact of disease and treatment factors on domains that are not commonly assessed, such as eating and drinking behavior, intimacy, self-expression, religious or spiritual activities, and financial situation.

Conclusion

The present study is the first to examine illness intrusiveness and its relationship to SCD-related symptoms and HRQoL in adults with SCD. More severe fatigue, depressive, and anxiety symptoms were related to greater illness intrusiveness, with fatigue emerging as an independent predictor of illness intrusiveness. Furthermore, greater illness intrusiveness is associated with compromised physical and mental HRQoL. This highlights that fatigue is an important SCD symptom with significant clinical and functional implications. These findings are especially relevant for psychologists in medical and rehabilitation settings conducting assessments and interventions with this population. Assessments and interventions that target fatigue management hold promise for reducing illness intrusiveness and ultimately improving HRQoL in adults with SCD.

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Data Availability Data are available by request from the corresponding author.

Code Availability Not applicable.

Declarations

Competing Interests The authors have no competing interests to disclose that are relevant to the content.

Ethical Approval The study procedures were approved by the University of Maryland, Baltimore County's institutional review board.

Consent to Participate All individuals provided informed consent to participate in the study.

Consent for Publication All individuals provided informed consent for publication of deidentified data.

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