

# The burden of iron overload in sickle cell disease: insights from South Carolina, USA.

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**Keywords:** Anemia; Sickle Cell; Iron Overload; Liver Iron Concentration; Ferritin; Liver Function Tests; Chelation Therapy.

**Abstract.** Red blood cell transfusions can lead to iron overload (IO) in sickle cell disease (SCD). We aimed to determine the relationship between SCD patients with IO and SCD comorbidities. Iron chelation regimen for IO in SCD patients was also studied. A cohort of 245 SCD adult patients receiving care at the Medical University of South Carolina (MUSC) was studied. Information was obtained from medical records. Statistical analysis was performed to examine correlations and odds ratios with 95% confidence intervals. We identified 85 (34.7%) participants who met IO criteria. The results showed a significant association of IO with stroke (OR= 14.67, p= 0.0001), pulmonary hypertension (OR= 4.75, p= 0.0006), acute chest syndrome (OR= 2.46, p= 0.003), and deep vein thrombosis (OR= 1.84, p= 0.04). There was a strong correlation between liver iron concentration (LIC) and ferritin levels (r= 0.5148, p<0.0001). Liver enzymes correlated well with LIC and ferritin levels. Eighty-six percent of participants (74/85) were on chelation therapy, but only 19% of them achieved a good response to the treatment. One-third of SCD individuals developed IO, associated with several comorbidities. Comprehensive measures must include periodic determinations of LIC and ferritin, followed by appropriate chelation therapy to prevent organ damage.

## La sobrecarga de hierro en la anemia falciforme: perspectivas desde Carolina del Sur, EEUU.

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**Palabras clave:** Anemia de Células Falciformes; Sobrecarga de Hierro; Concentración Hepática de Hierro; Ferritina; Pruebas de Función Hepática; Terapia por Quelación.

**Resumen.** Las transfusiones de glóbulos rojos pueden provocar sobrecarga de hierro (SH) en la enfermedad de células falciformes (ECF). Nuestro objetivo fue determinar la relación entre pacientes con ECF con SH y comorbilidades asociadas a la ECF. También se estudió el régimen de quelación de hierro para la SH en pacientes con ECF. Se estudió una cohorte de 245 pacientes adultos con ECF atendidos en la Medical University of South Carolina (MUSC). La información se obtuvo de las historias clínicas. Se realizó un análisis estadístico para analizar las correlaciones y las razones de probabilidades (odds ratios) con intervalos de confianza del 95%. Se encontraron 85 (34,7%) participantes con criterios de SH. Los resultados mostraron una asociación significativa de la SH con el ictus (OR = 14,67,  $p = 0,0001$ ), la hipertensión pulmonar (OR = 4,75,  $p = 0,0006$ ), el síndrome torácico agudo (OR = 2,46,  $p = 0,003$ ) y la trombosis venosa profunda (OR = 1,84,  $p = 0,04$ ). Se observó una fuerte correlación entre la concentración hepática de hierro (CHH) y el nivel de ferritina ( $r = 0,5148$ ,  $p < 0,0001$ ). Las enzimas hepáticas se correlacionaron adecuadamente con la CHH y los niveles de ferritina. El 86% de los participantes (74/85) recibía terapia de quelación, pero solo el 19% obtuvo una buena respuesta al tratamiento. Un tercio de los pacientes con enfermedad de células falciformes desarrolló sobrecarga de hierro asociada a diversas comorbilidades. Las medidas integrales deben incluir determinaciones periódicas de la CHH y la ferritina, seguidas de un tratamiento de quelación adecuado para prevenir el daño orgánico.

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### INTRODUCTION

Sickle cell disease is a common hemoglobinopathy, and approximately 4,000 people in South Carolina, USA, live with this disease (SCD) <sup>1</sup>. In the management of SCD, chronic transfusion therapy is used to prevent and treat complications <sup>2</sup>. Each unit of transfused packed red blood cells (pRBCs) provides 200-250 mg of iron, and repeated blood transfusions will lead to iron overload (IO) in SCD patients. Previous studies have

shown that the IO resulting from transfusional therapy in other patient populations is associated with significant morbidity and mortality <sup>3</sup>. Iron overload has been considered a major cause of end-organ damage in multitransfused patients with hemoglobinopathies <sup>4</sup>, and the source of excessive iron burden in SCD is primarily blood transfusions and intravascular hemolysis.

To assess the degree of IO, liver iron concentration (LIC) can be measured invasively via liver biopsy or noninvasively by

magnetic resonance imaging (MRI). There is a very close correlation between the two methods; thus, MRI has largely eliminated the need for liver biopsies<sup>5</sup>. Ferritin should be used as a measure of IO in SCD patients, but its values should be interpreted with caution for therapeutic decision-making<sup>6</sup>. Iron accumulation depends on the age at which blood transfusions are started, the rate of transfusions, and the nature of the transfusion regimen<sup>7</sup>. Compared with thalassemia, iron deposition in cardiac, renal, or endocrine organs is lower in SCD because intravascular hemolysis promotes biliary and urinary elimination of iron as hemosiderin, heme, and hemoglobin, and the chronic inflammatory state reduces toxic accumulation of iron in macrophages<sup>7-9</sup>. Additionally, there is a difference between multiple simple transfused SCD patients and patients receiving blood with exchange transfusions because there is less liver accumulation of transfused iron in the latter<sup>8,9</sup>.

It is complicated to establish if organ damage is caused by iron from transfusion as a treatment for some SCD comorbidities or if damage is a consequence of the complications themselves<sup>5,6</sup>. The non-transferrin-bound iron free in plasma is toxic because it produces radicals with oxidation products that are responsible for a significant part of iron accumulation and cell injury associated with regular multiple transfusions. Additionally, inflammation, as a pathophysiologic mechanism in SCD, leads to increased hepcidin synthesis and decreased iron absorption, with increased iron retention in the reticulo-endothelial system<sup>9</sup>.

IO is known to increase morbidity and mortality in SCD, although the exact mechanism is unclear<sup>10-12</sup>. This risk of increased mortality could be associated with a high rate of comorbidities<sup>13</sup>. Except for the comorbidities of stroke or the presence of an abnormal transcranial doppler (TCD), whose preventive treatment is based on chronic transfu-

sions<sup>14</sup>, it is difficult to determine whether IO induces the presence of comorbidities or whether these comorbidities are independent of IO. It has been shown that in groups of SCD patients with IO, there was a higher mortality rate than those without IO. Those deaths were attributable to sudden death or pneumonia associated with acute chest syndrome<sup>13</sup>. The rate of admission for vasoocclusive crisis related to the prevalence of organ damage and SCD complications only found a meaningful relationship with IO and acute chest syndrome (ACS)<sup>15</sup>. Ferroptosis has also been recognized as a novel mechanism in SCD and an additional avenue for organ damage in SCD patients. In ferroptosis, elevated iron levels trigger cell death by increasing reactive oxygen species (ROS) and lipid peroxides, leading to organ impairment<sup>16</sup>.

Iron chelation is the primary treatment for IO in SCD, and it can be initiated if more than 18 transfusions have been received (or >120 cc/kg of PRBC) within a defined period. Additionally, a serum ferritin level >1000 ng/mL on two separate measurements, or hepatic MRI-quantified iron >3 mg/g of dry weight, indicates IO treatment. Because SCD causes a degree of chronic inflammation, ferritin, an acute-phase reactant, is less reliable as a diagnostic tool than in other anemias.

There are three iron chelators currently approved for clinical use: (1) deferoxamine (DFO), (2) deferiprone (DFP), and (3) deferasirox (DFX). DFO is the oldest drug and is administered intravenously or subcutaneously, while DFP and DFX are taken orally<sup>14,15</sup>.

The primary aim of this study was to determine the relationship between iron overload and comorbidities in SCD patients. The secondary aims included evaluating the association between liver iron concentration (LIC), serum ferritin levels, liver enzymes, and the characteristics of the iron chelation regimen in chronically transfused SCD patients.

## MATERIAL AND METHODS

We conducted a retrospective chart review of the electronic medical records (EMRs) of 245 adults with SCD who receive care at MUSC in Charleston, South Carolina, and are enrolled in the Sickle Cell Disease Implementation Consortium (SCDIC)<sup>17</sup>. The study participants had a diagnosis of SCD, were English-speaking, and aged 15-50. From that population, we identified 85 subjects with both SCD and iron overload (34.7%). EMR data were collected over seven years (2017-2024). The inclusion criteria for this study were a diagnosis of SCD, enrollment in the MUSC-SCDIC-II Registry and REAL Answers projects, and a diagnosis of IO using the previously mentioned parameters. Age, sex, genotype, blood ABO group, comorbidities, ferritin, LIC, liver enzymes, and iron chelation treatment were obtained from the EMR. Patients with iron overload who received a hematopoietic stem cell transplant were excluded from this study.

Institutional review board (IRB) approval was obtained from each of the eight study sites and a central IRB (CIRBI/Advarra) prior to data collection, and a written informed consent was obtained from each participant.

### Statistical Analysis

Statistical analysis was performed using GraphPad InStat3 (GraphPad Software, Boston, MA 02110) to analyze frequency distributions for categorical variables and to perform linear regression and Pearson correlation for continuous variables. A 2 x 2 contingency table was used to calculate odds ratios with 95% confidence intervals by Fisher's exact test and to calculate sensitivity and specificity parameters. The reference group for the odds ratio (OR) was adult SCD patients (160/245) without iron overload. A  $p < 0.05$  was considered statistically significant.

## RESULTS

Table 1 describes the demographic characteristics of the 85 (34.7%) subjects with SCD and IO who met inclusion criteria. Seventy-

three IO patients (85.9%) were between 18-45 years old with a median age of 32.5 years (range 16-55), 61.2% were female, 95.3% had SS genotype, and 56.5% had blood group O. From 67.0% with IO criteria receiving transfusions (57/85), 51% (29/57) were treated under manual blood exchange regimen, and the rest of them by erythrocytapheresis regimen.

The prevalence of several comorbidities with SCD is described in Table 2. Patients with IO were noted to have a higher rate of four comorbidities: acute chest syndrome (OR= 2.46,  $p = 0.003$ ), deep vein thrombosis (DVT, OR= 1.84,  $p = 0.04$ ), stroke (OR= 14.67,  $p = 0.0001$ ) and pulmonary hypertension (PH, OR= 4.75,  $p = 0.0006$ ), seen in Table 2 and Fig. 1. Pulmonary hypertension (PH) was defined as a mean pulmonary arterial pressure of at least 25 mm Hg, and a TRV  $> 2.5$  m/s.

### MRI studies, liver biopsy, LIC, and ferritin

Seventy-four percent of subjects with IO initially had MRI/LIC records available (63/85) and 26% had also liver biopsy data available (22/85). Twenty-four percent (20/85) of them did not have a subsequent record of LIC, as measured by liver MRI or liver biopsy, and were followed only with ferritin determination. Cardiac MRI data were available for 25% (21/85) of subjects, and only one patient showed myocardial iron deposition.

The average values at the start and end of the study for LIC were  $11.71 \pm 8.46$  mg/g dry weight ( $n = 59$ ) and  $12.88 \pm 7.86$  mg/g dry weight ( $n = 44$ ), respectively; the average values for ferritin were  $3779.5 \pm 2852$  ng/mL ( $n = 85$ ) and  $5055.1 \pm 5567.4$  ng/mL ( $n = 85$ ), respectively;  $p = 0.06$  for both.

There was a strong correlation between LIC (mg/g dry weight) and ferritin level (ng/mL) ( $r = 0.5148$ ,  $p = 0.0001$ ), as seen in Fig. 2. We also observed a strong correlation between serum ferritin and LIC in individuals with serum ferritin levels  $> 2500$  ng/mL ( $r = 0.5220$ ,  $p = 0.0026$ ,  $n = 31$ ). There was no correlation in patients with serum ferritin levels below 2500 ng/mL ( $r = 0.3133$ ,  $p = 0.3213$ ;  $n = 12$ ).

**Table 1.** Demographic characteristics of Iron overload in Sickle Cell Disease.

Characteristics	Iron Overload (N=85)	No Iron Overload (N=160)	Total (N=245)
Age group (years)			
<18	4 (4.7%)	10 (6.3%)	14 (5.7%)
18-24	20 (23.5%)	22 (13.7%)	42 (17.2%)
25-34	24 (28.2%)	65 (40.6%)	89 (36.3%)
35-45	29(34.2%)	43 (26.9%)	72 (29.4%)
>45	8(9.4%)	20 (12.5%)	28 (11.4%)
Median	32.5	31.0	32.0
Gender			
Male	34 (40.0%)	62 (38.8%)	96 (39.2%)
Female	51 (60.0%)	98 (61.2%)	149 (60.8%)
Age (N)			
Male	31.36±10.4 (34)	34.36±11.0 (62)	33.33±10.8(96)
Female	33.43±9.4 (51)	32.51±11.1 (98)	32.75±10.7(149)
Mean±SD	32.61±9.8 (85)	33.26±11.2 (160)	33.05±10.7 (245)
SCD Genotype			
SS	81 (95.3%)	98 (61.3%)	179 (73.1%)
SC	1 (1.2%)	40 (25.0%)	41 (16.7%)
SThal	3 (3.5%)	19 (11.9%)	22 (9.0%)
Other	0 (0%)	3 (1.8%)	3 (1.2%)
Blood Group (ABO)			
Group O	48 (56.5%)		
Group A	20 (23.5%)		
Group B	10 (11.8%)		
Group AB	7 (8.2%)		

**Table 2.** Sickle Cell Disease Iron overload and comorbidities relationships.

Comorbidity	IO (N=85)	No IO (160)	Total (N=245)	OR (CI95%)	OR p-value
ACS	65 (26.5%)	91 (37.1%)	156(63.7%)	2.46 (1.37-4.45)	<b>0.0032</b>
DVT	33 (12.2%)	41 (18.0%)	74(30.2%)	1.84 (1.05-3.23)	<b>0.0406</b>
Retinopathy	13 (5.3%)	42 (17.1%)	55 (22.4%)	0.50 (0.26-1.01)	0.0548
Stroke*	46(18.8%)	13 (5.3%)	59(24.1%)	13.34 (6.56-27.12)	<b>0.0001</b>
CKD	20 (7.8%)	25 (10.2%)	45 (17.9%)	1.66 (0.86-3.21)	0.1650
Anxiety/Depression	39 (16.7%)	61 (23.3%)	100(40.0%)	1.38 (0.80-2.34)	0.2752
AVN	42 (17.1%)	62(25.3%)	104 (42.4%)	1.54 (0.91-2.63)	0.1351
Pulmonary Htn	17 (7.8%)	8(2.9%)	25 (10.7%)	4.75 (1.96-11.54)	<b>0.0006</b>

ACS: Acute Chest Syndrome; DVT: Deep Vein Thrombosis; CKD: Chronic Kidney Disease; AVN: Avascular Necrosis; Htn: Hypertension. \*Include overt stroke and abnormal transcranial doppler (TCD).

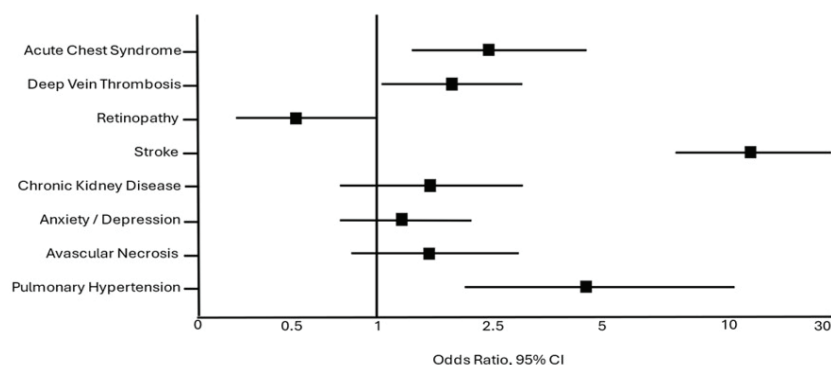


Fig. 1. Odds Ratio for Comorbidities in Sickle Cell patients with IO.

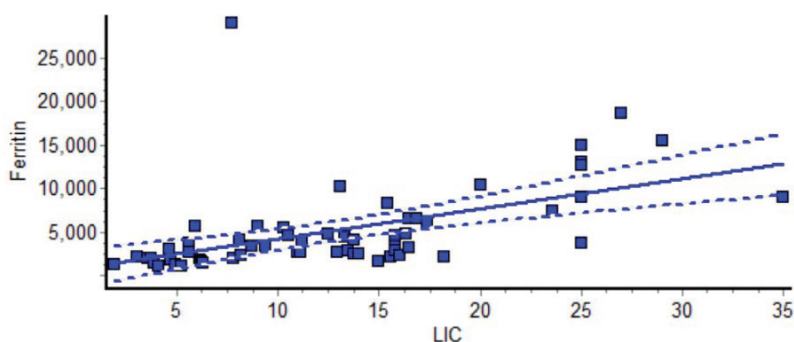


Fig. 2. Linear regression with 95%CI between LIC (mg/g dry weight) and Ferritin (ng/mL) in SCD participants (n=59) diagnosed as Iron overload,  $r = 0.5148$ ,  $p < 0.0001$ .

An increasing number of comorbidities was associated with rising LIC and serum ferritin (Table 3). The median number of co-morbidities per patient was 3 (mean  $3.12 \pm 1.5$ ).

#### Accuracy estimation of ferritin as a marker of iron overload in SCD participants

Among 69 IO subjects with paired LIC and ferritin levels, 36 had a LIC  $\geq 10$  mg/g dw and 23 had a LIC  $< 10$  mg/g dw. Using a ROC curve and a serum ferritin cut-off of  $\geq 2500$  ng/mL, we obtained 78% sensitivity, 74% specificity, 86% positive predictive value, and 61% negative predictive value. In our patient sample, 46 subjects were correctly diagnosed with IO based on their serum ferritin levels (TP), and 13 patients were incorrectly identified as not having IO (FN). The accuracy of the serum ferritin level to

diagnose IO was 76% and the area under the curve (AUC) was 76% (Table 4), (Garcia-Casal et al. <sup>18</sup>).

#### Iron overload and liver enzymes

In SCD individuals with IO, liver enzymes showed a good correlation with LIC and ferritin levels (Supplemental Table 5), except for alkaline phosphatase and LIC. The mean serum values  $\pm$  SD were AST:  $47.8 \pm 26.32$  U/L, ALT:  $33.86 \pm 27.36$  U/L, and AP:  $113.66 \pm 55.12$  U/L.

#### Iron chelation treatment

Transfused patients with IO received an average of 22 pRBCs per year with a median of 12 transfusions. Eighty-six percent (74/85) were prescribed chelation therapy with deferasirox (DFX), and two patients were prescribed deferoxamine (DFO) chelation therapy. Of those on che-

**Table 3.** Values of LIC and ferritin associated with the number of comorbidities in subjects with Iron overload.

No comorbidities	LIC (N=43)	Ferritin (N=85)	<i>p</i>
1	11.58±5.2 (7)	5538.28±7793.6 (9)	0.0661
2	14.82±7.6 (17)	5748.89±5336.7 (29)	0.0001
3	12.83±9.6 (6)	7026.32±7608.4 (15)	0.0031
4	7.74±4.37 (5)	2588.65±2552.1 (14)	0.0023
>5	11.58±8.17 (8)	3936.66±3800.9 (18)	0.0004

LIC: liver iron concentration (mg/g dry weight), ferritin (ng/mL).

**Table 4.** Sensitivity and specificity of ferritin as a marker in Sickle Cell Disease to assess iron overload (N=69).

Variable	Value	95% Confidence Interval
Sensitivity	0.7750	0.6159 to 0.8917
Specificity	0.7368	0.4879 to 0.9085
Positive Predictive Value	0.8611	0.7052 to 0.9533
Negative Predictive Value	0.6087	0.3856 to 0.8027
Likelihood Ratio	2.945	
DOR	9.65	

DOR: diagnostic odds ratio, calculated as the effectiveness as an index of iron overload<sup>18</sup>.  $DOR = (\text{sens} \times \text{spec}) / (1 - \text{sens}) \times (1 - \text{spec}) = (\text{sens} \times \text{spec}) / (\text{FNs}) \times (\text{FPs})$ .

lation therapy with deferasirox, only 19% (14/74) obtained a good response with serum ferritin <1000 ng/mL. Providers followed 54% of these patients with periodic LIC determinations and serum ferritin (40/74), and the remaining patients were followed with serum ferritin alone. Information about the side effects of DFX treatment was scarce and difficult to collect from the data records. Fifty-four percent (40/74) of the subjects were on disease-modifying treatment.

## DISCUSSION

These findings show a significant association of IO with several comorbidities in a cohort of SCD patients. Most of the patients were SS genotype young adults receiving fre-

**Table 5.** Correlations between LIC and ferritin versus liver enzymes.

Variable (N)	<i>r</i>	<i>p</i>
LIC vs AST (43)	0.5551	<b>0.0001</b>
LIC vs ALT (43)	0.5248	<b>0.0003</b>
LIC vs AP (43)	0.1393	0.3730
Ferritin vs AST (85)	0.5794	<b>0.0001</b>
Ferritin vs ALT (85)	0.6015	<b>0.0001</b>
Ferritin vs AP (85)	0.3644	<b>0.0006</b>

LIC: liver iron concentration; AST: aspartate transferase; ALT: alanine aminotransferase; AP: alkaline phosphatase. The values of liver enzymes were expressed in U/L, LIC in mg/g dry weight, and ferritin in ng/mL. The reference ranges for liver enzymes were AST (5-34 U/L), ALT (5-45 U/L) and AP (35-150 U/L).

quent blood transfusions. Parameters such as LIC, measured by MRI and/or liver biopsy, were used to diagnose IO in many of these patients, and serum ferritin levels were used as a marker of IO. There was a strong correlation between LIC and serum ferritin when the serum ferritin levels were above 2500 ng/mL. Liver enzymes showed a good correlation with LIC and serum ferritin levels, and chelation therapy with DFX was unsuccessful in most cases.

Previous research has demonstrated that SCD patients with IO have an increased risk of mortality<sup>11,12</sup>, and this risk could be associated with a high rate of comorbidities<sup>13</sup>. Moreover, liver injury is associated with mortality in SCD, with increased ferritin and direct bilirubin as predictors of mor-

tality. All patients with advanced liver fibrosis had IO, but not all patients with IO had fibrosis<sup>19</sup>. We have seen an increased number of comorbidities in our study patients with IO, and so this condition may be a predisposing factor for increased morbidity and mortality in SCD patients. In our study, five (2.0%) patients with SCD died, and three of those had IO.

As demonstrated previously<sup>20</sup>, our findings showed a stroke or at-risk-of-stroke prevalence of 24% (59/245) in SCD patients. Of the patients with stroke or at risk of stroke, 78% of them had IO (70% stroke, 30% abnormal TCD), making stroke the most common comorbidity that we observed with IO. This high rate of IO could be explained by the use of frequent blood transfusion as primary or secondary prevention in SCD individuals with abnormal TCD or cerebrovascular event<sup>14</sup>. In our study population, none of these patients had recurrent strokes after the initial event.

Sixty-four percent of our study population had ACS, and 41.6% of patients with ACS also had IO. In this population, patients with IO were at a significantly higher risk of ACS. This relationship, at least in part, may be related to the use of simple blood transfusions to improve oxygen-carrying capacity in persons with symptomatic ACS, and to the urgent exchange transfusion performed when there is rapid progression of ACS<sup>21,22</sup>.

The prevalence of DVT was 30.2% (74/245) in individuals with SCD, with a predominance in the female sex (66.2%), as has also been described in one other study<sup>23</sup>. A significant relationship between IO and DVT could be explained by the occurrence of a hypercoagulable state in individuals with SCD<sup>24</sup>, driven by inflammation, in part due to oxidative stress and iron deposition-induced ferroptosis, leading to thrombogenesis and activation of the coagulation cascade in SCD individuals<sup>25</sup>.

Epidemiological studies reveal that PH development is associated with iron overload and other comorbidities<sup>26</sup>. Chronic anemia

in sickle cell disease results in cardiac chamber dilation and a compensatory increase in left ventricular mass. Elevated TRV as well as ferritin and the number of red blood cell units transfused, were also found to be associated with a higher risk of death<sup>27</sup>. In the current study, we found that the prevalence of IO associated with PH, as diagnosed by echocardiography, was 7.8%. Additionally, patients with IO were statistically more likely to have PH, with 68% of patients with PH also having IO.

In this study, there was no significant association between IO and other comorbidities such as anxiety and depression. However, we found a 40% prevalence of these mental health issues in the entire cohort of SCD patients. Depression is prevalent in adult patients with SCD and is associated with worse health-related quality of life, so an assessment of anxiety and depression in persons living with SCD is vitally important, given the prevalence of this comorbidity in the general SCD population<sup>12,28</sup>.

The relationship between IO and acute kidney injury (AKI) and chronic kidney disease (CKD), although it was not significant in our study, may be a subject of further studies due to the risk of toxicity by iron chelation treatment with an elevated risk of mortality in SCD individuals<sup>29</sup>. Recently, ferroptosis has been implicated in the development of AKI/CKD, as renal cells are particularly vulnerable to IO<sup>30</sup>.

Usually, follow-up of patients with SCD and IO is based on periodic MRI measurements of LIC and serum ferritin levels. The current study has demonstrated a strong correlation between LIC and ferritin levels above 2500 ng/mL, with a sensitivity of 78% and a specificity of 74%. This correlation is compatible with other studies<sup>6</sup>. Additionally, this threshold could indicate the need for chelation treatment if LIC cannot be performed<sup>31</sup>. However, when the serum ferritin level is less than 2500 ng/mL, it is less reliable as a marker of LIC. This may be related to serum ferritin levels being af-

ected by chronic inflammation in SCD. Especially during an acute exacerbation of a comorbidity or a vasoocclusive event, serum ferritin may be less reliable for estimating LIC<sup>32</sup>. Additionally, it is important to note that only one-third of the subjects in our study with SCD and elevated serum ferritin levels underwent MRI for LIC measurement, reflecting a lack of appropriate follow-up for screening, diagnosis, and treatment of IO. This observation is in agreement with other studies<sup>31</sup>.

Liver enzymes, as a measure of liver function, correlated well with serum ferritin and LIC levels in the SCD cohort with IO. Alkaline phosphatase has been associated with mortality<sup>19</sup>, and some studies have reported a correlation between serum ferritin and AST as an estimator of LIC. A serum ferritin/AST ratio  $>17 \mu\text{g}/\text{U}$  has been highly predictive of IO<sup>33</sup>. Nevertheless, in the population, routine screening of liver enzymes has poor sensitivity and specificity for detecting liver damage<sup>34</sup>.

As shown in our study, IO is associated with a greater number of comorbidities. Thus, treating IO intuitively makes sense to reduce the risks associated with this condition. We found that DFX was the most commonly prescribed treatment for IO. Although 86% of IO patients in our study population were prescribed DFX, only 19% achieved ferritin levels  $<1000 \text{ ng/mL}$  during the study period. According to other references<sup>8,15,35</sup>, one factor contributing to a limited response to this treatment is poor adherence. While we did not assess compliance with chelation treatment as a cause of poor response in our study, treatment compliance is an important factor and should be evaluated when treating a patient for IO.

This study has several limitations: its observational, retrospective, and cross-sectional design, along with the reliance on medical record abstraction and the patient's self-report of symptoms, could introduce bias and affect the statistical power of the results. In some cases, the evolution of IO is represented solely by serial determinations

of serum ferritin, without a matched LIC, and by periodic MRIs. Additionally, it was not distinguished whether the serum ferritin values were reported during vasoocclusive crisis or in the steady state of the patients, thus there is a risk that the vasoocclusive event could confound elevated serum ferritin levels. It is well known that ferritin levels increase significantly during a vaso-occlusive crisis<sup>9</sup>. Information on toxicities related to DFX treatment was scarce and difficult to extract from the data records.

In conclusion, iron overload in SCD is a life-threatening condition, often associated with an increased number of comorbidities leading to a declining clinical course with an inadequate quality of life, hepatic complications and premature death. Management suggests that MRI screening for liver iron concentration should be performed every one to two years in patients with SCD receiving chronic transfusion therapy. Serum ferritin levels should be measured after each transfusion; this inexpensive blood test broadly correlates with total body iron burden and, due to its ease of acquisition, is a valuable tool for monitoring trends in iron burden over time<sup>31</sup>. A significant limitation for using ferritin levels as indicator of IO in SCD is that inflammation can raise ferritin levels irrespective of iron burden<sup>2</sup>. Providers should monitor patients and assess adherence with chelation therapy in the treatment of IO. Iron overload in SCD requires preventive care and close monitoring to avoid irreversible organ damage.

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### Conflict of interest statement

Authors declare no conflicts of interest.

### Ethical approval and informed consent

Institutional review board (IRB) approval was obtained from each of the eight study sites and a central IRB (CIRBI/Advarra) prior to data collection and written informed consent was obtained from each participant.

### Consent for publication

Informed consent included agreement to have de-identified data published and disseminated in accordance with publication guidelines for the Sickle Cell Disease Implementation Consortium (SCDIC).

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### Authors contributions

GV drafted the manuscript and performed the statistical analyses. CA, CF, HF, ND and SR contributed to the concept and design of the study and revised manuscript drafts. All the authors critically reviewed and approved the manuscript.

### REFERENCES

1. **Hassell KL.** Population Estimates of Sickle Cell Disease in the U.S. *Am J Prev Med.* 2010;38(4):S512-S521. <https://doi.org/10.1016/j.amepre.2009.12.022>.
2. **Chou ST, Alsawas M, Fasano RM, Field JJ, Hendrickson JE, Howard J, et al.** American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support. *Blood Adv.* 2020; 28;4(2):327-355. <https://doi.org/10.1182/bloodadvances.2019001143>.
3. **Harmatz P, Butensky E, Quirolo K, Williams R, Ferrell L, Moyer T, et al.** Severity of iron overload in patients with sickle cell disease receiving chronic red blood cell transfusion therapy. *Blood.* 2000;96(1):76-79. <https://doi.org/10.1182/blood.V96.1.76>.
4. **Theocharidou E, Suddle AR.** The Liver in Sickle Cell Disease. *Clin Liver Dis.* 2019;23(2):177-189. <https://doi.org/10.1016/j.cld.2018.12.002>.
5. **Coates TD, Wood JC.** How we manage iron overload in sickle cell patients. *Br J Haematol.* 2017;177(5):703-716. <https://doi.org/10.1111/bjh.14575>.
6. **Badawy SM, Liem RI, Rigsby CK, Labotka RJ, DeFreitas RA, Thompson AA.** Assessing cardiac and liver iron overload in chronically transfused patients with sickle cell disease. *Br J Haematol.* 2016;175(4):705-713. <https://doi.org/10.1111/bjh.14277>.
7. **Porter J, Garbowski M.** Consequences and management of iron overload in sickle cell disease. *Hematology Am Soc Hematol Educ Program.* 2013;2013(1):447-456. <https://doi.org/10.1182/asheducation-2013.1.447>.
8. **Noetzli LJ, Coates TD, Wood JC.** Pancreatic iron loading in chronically transfused sickle cell disease is lower than in thalassaemia major. *Br J Haematol.* 2011;152(2):229-233. <https://doi.org/10.1111/j.1365-2141.2010.08476.x>.
9. **Marsella M, Borgna-Pignatti C.** Transfusional iron overload and iron chelation therapy in thalassemia major and sickle cell disease. *Hematol Oncol Clin North Am* 2014;28(4):703-727, vi. <https://doi.org/10.1016/j.hoc.2014.04.004>.
10. **Fung EB, Harmatz P, Milet M, Ballas SK, De Castro L, Hagar W, et al; Multi-Center Study of Iron Overload Research Group.** Morbidity and mortality in chronically transfused subjects with thalassemia and sickle cell disease: A report from the

- multi-center study of iron overload. *Am J Hematol.* 2007;82(4):255-265. <https://doi.org/10.1002/ajh.20809>.
11. **Ballas SK.** Iron overload is a determinant of morbidity and mortality in adult patients with sickle cell disease. *Semin Hematol.* 2001;38 (1 Suppl 1):30-36. [https://doi.org/10.1016/S0037-1963\(01\)90058-7](https://doi.org/10.1016/S0037-1963(01)90058-7).
  12. **Njoku F, Pugh N, Brambilla D, Kroner B, Shah N, Treadwell M, et al.** Mortality in adults with sickle cell disease: Results from the sickle cell disease implementation consortium (SCDIC) registry. *Am J Hematol.* 2024;99(5):900-909. <https://doi.org/10.1002/ajh.27279>.
  13. **Piel FB, Jobanputra M, Gallagher M, Weber J, Laird SG, McGahan M.** Co-morbidities and mortality in patients with sickle cell disease in England: A 10-year cohort analysis using hospital episodes statistics (HES) data. *Blood Cells Mol Dis.* 2021; 89:102567. <https://doi.org/10.1016/j.bcmd.2021.102567>.
  14. **Webb J, Kwiatkowski JL.** Stroke in patients with sickle cell disease. *Expert Rev Hematol.* 2013;6(3):301-316. <https://doi.org/10.1586/ehm.13.25>.
  15. **van Tuijn CFJ, Schimmel M, Van Beers EJ, Nur E, Biemond BJ.** Prospective evaluation of chronic organ damage in adult sickle cell patients: A seven-year follow-up study. *Am J Hematol.* 2017;92(10):E584-E590. <https://doi.org/10.1002/ajh.24855>.
  16. **Fortuna V, Lima J, Oliveira GF, Oliveira YS, Getachew B, Nekhai S, et al.** Ferroptosis as an emerging target in sickle cell disease. *Curr Res Toxicol.* 2024;7:100181. <https://doi.org/10.1016/j.crttox.2024.100181>.
  17. **DiMartino LD, Baumann AA, Hsu LL, Kanter J, Gordeuk VR, Glassberg J, et al; Sickle Cell Disease Implementation Consortium.** The sickle cell disease implementation consortium: Translating evidence-based guidelines into practice for sickle cell disease. *Am J Hematol.* 2018;93(12):E391-E395. <https://doi.org/10.1002/ajh.25282>.
  18. **Garcia-Casal MN, Pasricha SR, Martinez RX, Lopez-Perez L, Peña-Rosas JP.** Serum or plasma ferritin concentration as an index of iron deficiency and overload. *Cochrane Database Syst Rev.* 2021;5(5): Cd011817. <https://doi.org/10.1002/14651858.CD011817>.
  19. **Feld JJ, Kato GJ, Koh C, Shields T, Hildesheim M, Kleiner DE, et al.** Liver injury is associated with mortality in sickle cell disease. *Aliment Pharmacol Ther.* 2015;42(7):912-921. <https://doi.org/10.1111/apt.13347>.
  20. **Verduzco LA, Nathan DG.** Sickle cell disease and stroke. *Blood.* 2009;114(25):5117-5125. <https://doi.org/10.1182/blood-2009-05-220921>.
  21. **Yawn BP, Buchanan GR, Afenyi-Annan AN, Ballas SK, Hassell KL, James AH, et al.** Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. *JAMA.* 2014;312(10):1033-1048. <https://doi.org/10.1001/jama.2014.10517>. Erratum in: *JAMA.* 2015;313(7):729.
  22. **Estcourt LJ, Hopewell S, Trivella M, Hambleton IR, Cho G.** Regular long-term red blood cell transfusions for managing chronic chest complications in sickle cell disease. *Cochrane Database Syst Rev.* 2019;2019(10):CD008360. <https://doi.org/10.1002/14651858.cd008360.pub5>.
  23. **Brunson A, Lei A, Rosenberg AS, White RH, Keegan T, Wun T.** Increased incidence of VTE in sickle cell disease patients: risk factors, recurrence and impact on mortality. *Br J Haematol.* 2017;178(2):319-326. <https://doi.org/10.1111/bjh.14655>.
  24. **Naik RP, Streiff MB, Haywood C, Nelson JA, Lanzkron S.** Venous Thromboembolism in Adults with Sickle Cell Disease: A serious and under-recognized complication. *Am J Med.* 2013;126(5):443-449. <https://doi.org/10.1016/j.amjmed.2012.12.016>.
  25. **Ma H, Huang Y, Tian W, Liu J, Yan X, Ma L, Lai J.** Endothelial transferrin receptor 1 contributes to thrombogenesis through cascade ferroptosis. *Redox Biol.* 2024; 70:103041. <https://doi.org/10.1016/j.redox.2024.103041>.
  26. **Gladwin MT, Sachdev V.** Cardiovascular abnormalities in sickle cell disease. *J Am Coll*

- Cardiol. 2012;59 (13):1123-1133. <https://doi.org/10.1016/j.jacc.2011.10.900>.
27. Gladwin MT, Barst RJ, Gibbs JS, Hildesheim M, Sachdev V, Nouraie M, et al, walk-PHaSST Investigators and Patients. Risk factors for death in 632 patients with sickle cell disease in the United States and United Kingdom. PLoS One. 2014;9(7):e99489. <https://doi.org/10.1371/journal.pone.0099489>.
  28. Adam SS, Flahiff CM, Kamble S, Telen MJ, Reed SD, De Castro LM. Depression, quality of life, and medical resource utilization in sickle cell disease. Blood Adv. 2017;1(23):1983-1992. <https://doi.org/10.1182/bloodadvances.2017006940>
  29. Kang H, Han M, Xue J, Baek Y, Chang J, Hu S, et al. Renal clearable nanochelators for iron overload therapy. Nat Commun 2019;10(1):5134. <https://doi.org/10.1038/s41467-019-13143-g>.
  30. Li S, Han Q, Liu C, Wang Y, Liu F, Pan S, et al. Role of ferroptosis in chronic kidney disease. Cell Commun Signal. 2024;22(1):113. <https://doi.org/10.1186/s12964-023-01422-8>.
  31. Wilson SR, Sears M, Williams E, Drapekin J, Sivakumar I, Padrino S, et al. GRNDaD investigators. Gaps in the diagnosis and management of iron overload in sickle cell disease: a 'real-world' report from the GRNDaD registry. Br J Haematol. 2021;195(5):e157-e160. <https://doi.org/10.1111/bjh.17762>.
  32. Puliyl M, Sposto R, Berdoukas VA, Hofstra TC, Nord A, Carson S, et al. Ferritin trends do not predict changes in total body iron in patients with transfusional iron overload. Am J Hematol. 2014;89(4):391-394. <https://doi.org/10.1002/ajh.23650>.
  33. Cippà PE, Boucsein I, Adams H, Krausenbuehl PA. Estimating Iron Overload in Patients with Suspected Liver Disease and Elevated Serum Ferritin. Am J Med. 2014;127(10):1011.e1-1011.e3. <https://doi.org/10.1016/j.amjmed.2014.03.016>.
  34. Ginès P, Castera L, Lammert F, Graupera I, Serra-Burriel M, Allen AM, et al. LiverScreen Consortium Investigators. Population screening for liver fibrosis: Toward early diagnosis and intervention for chronic liver diseases. Hepatology. 2022;75(1):219-228. <https://doi.org/10.1002/hep.32163>.
  35. Porter J, Bowden DK, Economou M, Tronec J, Ganser A, Habr D, et al. Health-Related Quality of Life, Treatment Satisfaction, Adherence and Persistence in  $\beta$ -Thalassemia and Myelodysplastic Syndrome Patients with Iron Overload Receiving Deferasirox: Results from the EPIC Clinical Trial. Anemia. 2012;2012:297641. <https://doi.org/10.1155/2012/297641>.