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# Incidence and risk factors of pain crisis after hematopoietic cell transplantation for sickle cell disease

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**Key Points**

- Recurrence of VOC requiring hospitalization or treatment occurs in 8.7% of patients after HCT with stable donor engraftment in SCD.
- GF, age at HCT, prior history of VOC, and donor type are major contributory factors for the recurrence of vaso-occlusive episodes.

Vaso-occlusive episodes (VOC) or pain crises are the most common indications for hematopoietic cell transplantation (HCT) for sickle cell disease (SCD). Elimination of pain crisis after HCT is an important patient-centered outcome and may improve understanding of the natural history of pain syndromes in SCD. We examined deidentified records of 763 patients followed-up for a median of 36.7 months (range, 0.3-168.6 months), with 69.6% patient's age <18 years at HCT, 83.3% patient's Karnofsky-Lansky performance score (KPS) ≥90, overall survival 92.9%, event-free survival 72.4%, graft failure (GF) 22.4%, AGVHD 21.4%, CGVHD 27%, and pain crisis 8.65%. On unadjusted logistic regression, increased risk of pain crisis after HCT was observed in patient's aged >10 years at HCT (range, 11-17 years; OR, 9.43; 95% CI, 3.20-27.79; $P < .0001$), in age ≥18 years (OR, 16.62; 95% CI, 5.85-47.16; $P < .0001$), in those with history of pain crisis 2 years before HCT (OR, 13.16; 95% CI, 4.08-42.42; $P < .0001$), alternate donors (haploidentical [OR, 4.80; 95% CI, 2.48-9.31; $P < .0001$], unrelated matched [OR, 2.71; 95% CI, 1.23-5.97; $P = .0132$], and mismatched unrelated [OR, 3.19; 95% CI, 1.44-7.05; $P = .0041$], and those with GF (n = 41 [5.37%]; OR, 7.15; 95% CI, 4.20-12.18; $P < .0001$). Pain crisis was less frequent with KPS of ≥90 (OR, 0.31; 95% CI, 0.18-0.55; $P < .0001$). Multivariable logistic regression models confirmed age at HCT, KPS, graft type, donor type, history of VOC 2 years before HCT, and GF as independent predictors of pain crisis after HCT and generated predictive models and nomograms for pain crisis after HCT for SCD, which can support shared decision making.

## Introduction

Hematopoietic cell transplantation (HCT) is increasingly being applied as a curative therapy for SCD. The first patient with SCD to undergo HCT received the treatment for a diagnosis of acute myeloid leukemia.[1] In the initial clinical trial, the indication for HCT for SCD was a history of stroke in 57% of the patients.[2] More recently, pain crisis has emerged as the primary reason for patients undergoing HCT for SCD.[3] Recurrent vaso-occlusive episodes (VOCs), also known as pain crises, which impairs quality of life, is a major motivating factor for consideration of HCT.[4] VOCs are the result of a multifactorial

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

process resulting from sickled red blood cells and the resultant combination of hypoxia/reperfusion injury, ischemic tissue damage, and inflammation. Patients with SCD may concurrently or separately suffer from other pain syndromes including chronic pain because of bone infarction, avascular necrosis of the femoral or humeral head, leg ulcers, chronic osteomyelitis, chronic neuropathic pain, or intractable chronic pain without evident pathology.[5] Although sickling may be abolished by the establishment of donor-derived erythropoiesis, other causes of pain syndromes may follow a different trajectory. Hence, the elimination of pain crisis after HCT is not only a crucial patient-centered outcome but also has the potential to contribute to a better understanding of the natural history of other chronic pain syndromes in SCD. Case series of HCT for SCD report a decrease in healthcare use for pain crisis, decreased pain interference, and a decrease in use of opioids after successful HCT.[6-9] Early-phase clinical trials of autologous genetically modified HCT have also reported dramatic reductions in severe pain crisis .[10-12] Understanding the incidence and contributory factors for the recurrence of pain crisis after HCT will likely aid shared decision making regarding HCT. Furthermore, the efficacy of HCT in alleviating pain crisis is likely to inform the discussion of the ethics, cost-effectiveness, and public policy about HCT for SCD. We therefore sought to determine the incidence and predictive factors of pain crisis after HCT for SCD by interrogating a large data set of patients undergoing HCT, which were reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) registry.

## Methods

We report a retrospective registry-based study of data on patients undergoing HCT for SCD between 1991 and 2021 in the United States with data submitted to the CIBMTR. The deidentified data set was obtained through the National Heart, Lung, and Blood Institute Biologic Specimen and Data Repository Information Coordinating Center and hosted on https://curesicklecell.rti.org. The CIBMTR maintains a research database to serve as a comprehensive data source that can be used to study cellular therapies, including HCT. As per the Stem Cell Therapeutic and Research Act of 2005, all US transplant centers are required to submit outcomes data on all allogeneic transplants, both related and unrelated, when either the stem cell donation or the transplant occurs within the United States. Figure 1 depicts the various forms required to be submitted by the transplant centers participating in the CIBMTR as part of the stem cell transplant outcomes database. Furthermore, the CIBMTR assigns patients to either a Transplant Essential Data (TED) track, which collects core (essential) data, or a Comprehensive Report Form (CRF) track that captures detailed disease- and treatment-related data.[13] Assignment to each track is done on submission of the initial pretransplantation TED form and

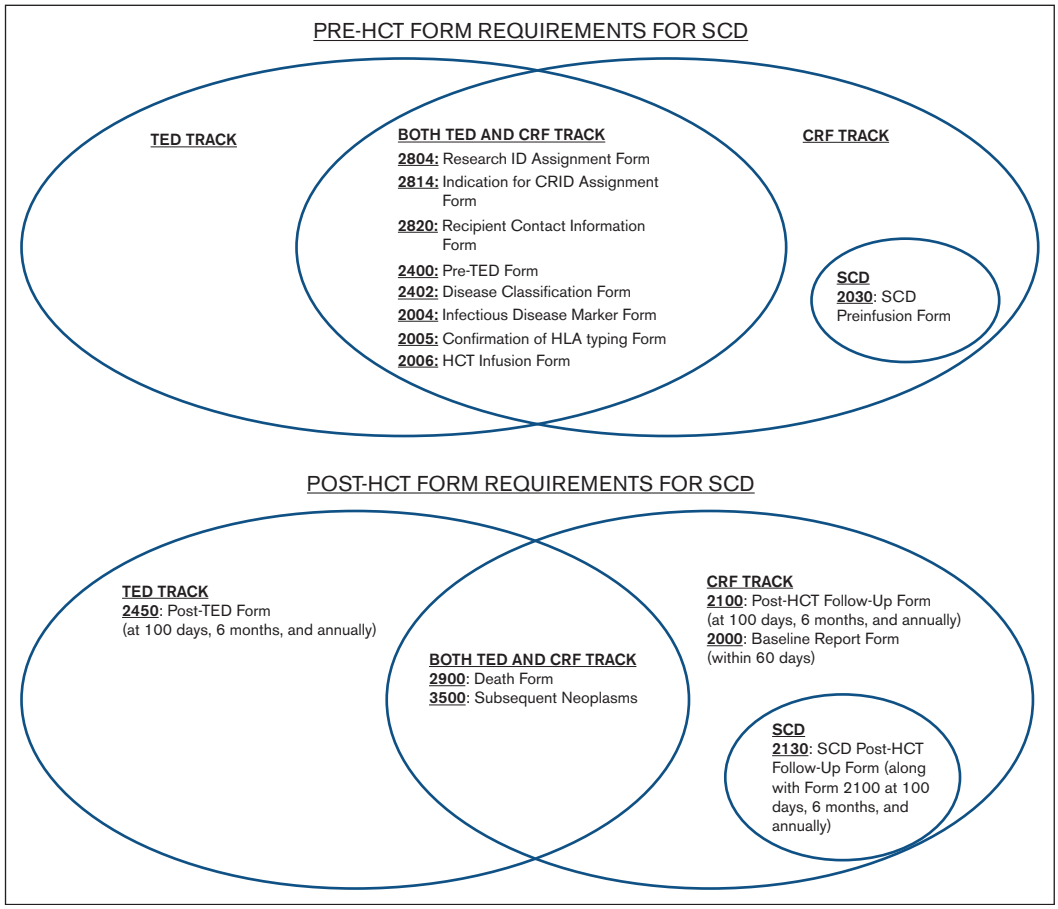


**Figure 1. Sources of HCT data.**

uses a weighted randomization algorithm designed to produce a cohort representative of current practice. All centers submit a Pre-HCT TED Form (Form 2400) for each allogeneic (related or unrelated) HCT. Additionally, a transplant center designated as a CRF center submits data on the Pre-TED Form, followed by either the Post-TED Form (Form 2450) or the CRF. The CIBMTR's form selection algorithm determines the type of follow-up form used for a specific recipient. Furthermore, for all recipients randomized to the CRF track whose primary disease is reported on the Pre-TED Disease Classification Form (Form 2402) as "Sickle Cell Disease (SCD)," centers are required to fill out the SCD Pre-Infusion Data Form (Form 2030) and the SCD Post-HCT Data Form (Form 2130). Data are collected at specific time points, including pre-transplantation and 3, 6, 12, and 24 months after HCT, and every 2 years until death, loss to follow-up, or last contact.

Instructions for completing the question on vaso-occlusive pain on the CIBMTR forms instruction manual (https://www.manula.com/manuals/cibmtr/fim/1/en/topic/q62-64-pain) states, "Vaso-occlusive pain, sometimes called a pain crisis, is a common painful complication of sickle cell disease in adolescents and adults." CIBMTR forms instruction manual offers no option to report other pain syndromes in patients with SCD, it is therefore likely that these are also included in the category of VOC. For the purpose of clarity, we therefore substitute the equivalent phrase "pain crisis" in the post-HCT setting, for VOC, because it is inclusive of all causes of sickle cell–related pain contributing to the need for treatment or hospitalization. The SCD Pre-Infusion Data Form (Form 2030) captures SCD-specific preinfusion data. Data specific to VOC pre-HCT were obtained from a question: "Did the recipient experience vaso-occlusive pain requiring hospitalization or treatment within the last 2 years?" A VOC episode was defined as any vaso-occlusive pain requiring hospitalization or treatment (ie, emergency room [ER] admission, day hospital, inpatient admission, etc). Furthermore, only VOCs requiring hospitalization or treatment in the hospital setting were included. The current form is not designed to capture patient-reported VOC that did not require ER, day hospital, or inpatient treatment. If the answer to this question was "yes," the next question captured the number of vaso-occlusive pain episodes the recipient experienced in the last 2 years and was reported as "≥3 instances/year," "<3 instances/year," or "Unknown." However, additional data regarding the treatment of the VOC episodes were not captured in the form.

After the HCT, the SCD Post-HCT Data Form (Form 2130) is completed along with each Post-HCT Follow-up Form (Form 2100) and is designed to capture specific data occurring within the timeframe of each reporting period (ie, between day 0 and day 100; between day 100 and the 6-month date of contact for the 6-month follow-up; and between the date of contact for the 6-month follow-up and the date of contact for the 1-year follow-up; etc). Form 2130 version 2.0 asks whether the recipient experienced vaso-occlusive pain requiring hospitalization or treatment (ie, ER admission, day hospital admission, inpatient admission, etc) since the last report. If the answer was "yes," the next question asks whether the number of instances of VOC was "<3/year," "≥3/year," or "unknown." More detailed information regarding VOC will likely be available in the future because the CIBMTR Form 2130 version 3.0, released in July 2021, includes additional questions, such as whether there is any new onset of chronic pain and whether opioids were prescribed for the treatment of pain.

A total of 1718 patients with SCD underwent a first allogeneic HCT between 1991 and 2021, with a median year of HCT of 2015. Of 1718 patients, 265 underwent HCT from 1991 to 2007 with no data on pain crisis after HCT in the HCT for SCD data set (reported as a value of "Unknown"). The remaining 1453 patients underwent HCT from 2008 to 2021, and 763 were assigned to the CRF track, with post-HCT data being available in Form 2130 version 2.0. As such, this cohort is the subject of the current study. Data for the rest of the 690 of 1453 patients were not reported because they were assigned to the TED track and were recorded as an "Unknown" on the form.

Patient characteristics before and after HCT, including demographics, are summarized in Table 1. A 2-sample *t* test was conducted to compare the difference in the mean of each continuous factor, and a $\chi^2$ test was used to assess the difference in the distribution of a categorical variable between patients having pain crisis after HCT and patients with no pain crisis after HCT. Univariable logistic regression models were used to detect the risk factors of pain crisis after HCT. The examined factors included but were not limited to patient demographics; age; height, weight; and pre-HCT variables such as hemoglobin (Hb) preconditioning, Karnofsky-Lansky performance score (KPS) at HCT, donor and graft type, conditioning intensity, the use of alemtuzumab, history of pain crisis 2 years before HCT, and the recipient cytomegalovirus status. We also examined post-HCT variables such as graft failure (GF), acute graft-versus-host disease (GVHD), chronic GVHD, and avascular necrosis. Variables with *P* values <0.1 were chosen as candidate variables for multivariable logistic regression models. Two multivariable logistic regression models were built using backward Akaike information criterion selection procedures; 1 focusing on using pretransplant factors, and another model focusing on using both pretransplant and posttransplant factors. In each model, a receiver operating characteristic curve was shown to evaluate the discriminative performance of the model, and a nomogram was created to visually examine the relationship between risk factors and the risk of pain crisis after HCT. The calibration and discrimination of the final multivariable logistic regression models were internally validated using bootstrapping methods (500 random selections with replacement from the main data set), and a *P* value <.05 was considered statistically significant. All analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC) and R (version 4.3.1).

## Results

Of 763 patients on the CRF track, 66 patients (8.65%) developed pain crisis after HCT. Patients were followed-up for a median of 36.7 months (range, 0.3-168.6 months); 69.6% of patients were aged <18 years at HCT, and 83.3% reported a KPS of ≥90. The 3-year overall survival was 92.9%; and the 3-year event-free survival, defined as the absence of GF or death (sustained donor engraftment with donor chimerism of >5% or Hb S level of <30%), was 72.4%. GF occurred in 171 patients (22.4%). Acute GVHD grades 2 to 4 occurred in 21.4%, and chronic GVHD developed in 27%. Of 66 patients with pain crisis after HCT, 41 had GF (62.12%), whereas 25 (37.88%) had pain crisis despite stable engraftment. The age at HCT of patients with GF who did not have pain crisis was lower (median age, 11 years) compared with patients with GF who developed pain crisis after HCT (median age,

**Table 1. Demographics of patients with information submitted on CRF regarding post-HCT pain crisis (n = 763)**

| | Post-HCT pain crisis | | Total | *P* value |
|---|---|---|---|---|
| | Yes (n = 66) | No (n = 697) | (n = 763) | |
| **Age (y) at transplant** | | | | <.001 |
| <10 | 4 (1.24%) | 319 (98.76%) | 323 (42.33%) | |
| 11-17 | 22 (10.58%) | 186 (89.42%) | 208 (27.26%) | |
| ≥18 | 40 (17.24%) | 192 (82.76%) | 232 (30.41%) | |
| **Sex** | | | | .93 |
| Male | 36 (8.74%) | 376 (91.26%) | 412 (54%) | |
| Female | 30 (8.55%) | 321 (91.45%) | 351 (46%) | |
| **KPS** | | | | |
| Missing | 5 | 8 | 13 | <.001 |
| <90 | 22 (17.60%) | 103 (82.40%) | 125 (16.67%) | |
| ≥90 | 39 (6.24%) | 586 (93.76%) | 625 (83.33%) | |
| **Donor type** | | | | <.001 |
| HLA identical sibling | 15 (3.97%) | 363 (96.03%) | 378 (49.54%) | |
| HLA mismatched sibling | 27 (16.56%) | 136 (83.44%) | 163 (21.36%) | |
| Matched unrelated | 12 (10.08%) | 107 (89.92%) | 119 (15.60%) | |
| Mismatched unrelated | 12 (11.65%) | 91 (88.35%) | 103 (13.50%) | |
| **Graft type** | | | | .007 |
| Bone marrow | 35 (6.86%) | 475 (93.14%) | 510 (66.84%) | |
| Peripheral blood | 22 (15.17%) | 123 (84.83%) | 145 (19%) | |
| Unrelated cord blood | 9 (8.33%) | 99 (91.67%) | 108 (14.15%) | |
| **Conditioning intensity** | | | | <.001 |
| Myeloablative | 15 (4.37%) | 328 (95.63%) | 343 (44.95%) | |
| Reduced intensity | 24 (7.67%) | 289 (92.33%) | 313 (41.02%) | |
| Nonmyeloablative | 27(25.23%) | 80 (74.77%) | 107 (14.02%) | |
| **Recipient CMV serostatus** | | | | .028 |
| Positive | 42 (10.85%) | 345 (89.15%) | 387 (50.72%) | |
| Negative | 24 (6.38%) | 352 (93.62%) | 376 (49.28%) | |
| **ACS before conditioning** | | | | .015 |
| Missing | 0 | 34 | | |
| Yes | 49 (11.16%) | 390 (88.84%) | 439 (60.22%) | |
| No | 17 (5.86%) | 273 (94.14%) | 290 (39.78%) | |
| **Pain crises 2 y before HCT** | | | | <.001 |
| Missing | 3 | 52 | 55 | |
| Yes | 60 (13.36%) | 389 (86.64%) | 449 (63.42%) | |
| No | 3 (1.16%) | 256 (98.84%) | 259 (36.58%) | |
| **Frequency of hospitalizations for pain crises** | | | | .015 |
| Missing | 19 | 373 | 392 | |
| <3/y | 14 (8.14%) | 158 (91.86%) | 172 (46.36%) | |
| ≥3/y | 33 (16.58%) | 166 (83.42%) | 199 (53.64%) | |
| **Acute GVHD** | | | | .63 |
| Yes | 15 (9.20%) | 148 (90.80%) | 163 (21.36%) | |
| No | 51 (8.63%) | 540 (91.37%) | 591 (77.46%) | |
| Acute GVHD, grade unknown | 0 | 9 | 9 (1.18%) | |
| **Chronic GVHD** | | | | .41 |
| Yes | 15 (7.28%) | 191 (92.72%) | 206 (27%) | |
| No | 51 (9.16%) | 506 (90.84%) | 557 (73%) | |

ACS, acute chest syndrome; AVN, avascular necrosis; CMV, cytomegalovirus.

**Table 1 (continued)**

| | Post-HCT pain crisis | | Total | *P* value |
|---|---|---|---|---|
| | Yes (n = 66) | No (n = 697) | (n = 763) | |
| **AVN** | | | | .20 |
| Missing | 6 | 36 | 42 | |
| Yes | 5 (14.29%) | 30 (85.71%) | 35 (4.85%) | |
| No | 55 (8.02%) | 631 (91.98%) | 686 (95.15%) | |
| **GF** | | | | <.001 |
| Yes | 41 (23.98%) | 130 (76.02%) | 171 (22.41%) | |
| No | 25 (4.22%) | 567 (95.78%) | 592 (77.59%) | |

ACS, acute chest syndrome; AVN, avascular necrosis; CMV, cytomegalovirus.

21 years) (Table 2). Similarly, the median age of patients with stable engraftment and pain crisis was higher (26 years) that that of those with no pain crisis after stable engraftment (11 years; Table 3).

Of 171 patients in the data set who had GF, 41 were reported to CIBMTR as having developed pain crisis, whereas 130 patients were not reported to have developed pain crisis . Factors that were associated with the risk of pain crisis in patients who developed GF included age at HCT ($P < .001$), age group at HCT ($P < .001$), weight before conditioning ($P < .001$), KPS at HCT ($P = .026$), conditioning intensity ($P < .001$), and a history of pain crisis in the 2 years before HCT ($P < .001$; Table 2). We compared those without GF who did (n = 25) or did not develop pain crisis (n = 567; Table 3). Age at HCT ($P < .001$), age group at HCT (<0.001), weight before conditioning ($P < .001$), donor type ($P < .001$), KPS at HCT ($P < .001$), conditioning intensity ($P < .001$) and history of pain crisis before HCT ($P < .006$) were significant risk factors predicting pain crisis after HCT.

Table 4 summarizes the results of univariable logistic regression for risk factors predictive of pain crisis after HCT. Using univariable

**Table 2. Comparison of risk factors for pain crises in those with GF (n = 171)**

| | GF with pain crisis (n = 41) | GF with no pain crisis (n = 130) | Total (n = 171) | *P* value |
|---|---|---|---|---|
| **Age at transplant, y (median)** | 21.0 | 11.0 | | <.001 |
| <10 | 2 (3.17%) | 61 (96.83%) | 63 (36.84%) | |
| 11-17 | 15 (31.25%) | 33 (68.75%) | 48 (28.07%) | |
| ≥18 | 24 (60%) | 36 (40%) | 60 (35.09%) | |
| Weight, kg (median) | 60.0 | 34.7 | | <.001 |
| **KPS** | | | | .026 |
| <90 | 11 (37.93%) | 18 (62.07%) | 29 (17.47%) | |
| ≥90 | 26 (18.98%) | 111 (81.02%) | 137 (82.53%) | |
| **Donor type** | | | | .18 |
| HLA identical sibling | 9 (14.75%) | 52 (85.25%) | 61 (35.67%) | |
| HLA mismatched relative | 14 (32.56%) | 29 (67.44%) | 43 (25.15%) | |
| Matched unrelated | 7 (26.92%) | 19 (73.08%) | 26 (15.20%) | |
| Mismatched unrelated | 11 (26.83%) | 30 (73.17%) | 41 (23.98%) | |
| **Graft type** | | | | .18 |
| Bone marrow | 19 (19.39%) | 79 (80.61%) | 98 (57.31%) | |
| Peripheral blood | 14 (34.15%) | 27 (65.85%) | 41 (23.98%) | |
| Umbilical cord blood | 8 (25%) | 24 (75%) | 32 (18.71%) | |
| **Conditioning intensity** | | | | <.001 |
| Myeloablative | 8 (13.33%) | 52 (86.67%) | 60 (35.09%) | |
| Reduced intensity | 15 (20.83%) | 57 (79.17%) | 72 (42.11%) | |
| Nonmyeloablative | 18 (46.15%) | 21 (53.85%) | 39 (22.18%) | |
| **Hisotry of pain crisis 2 y before HCT** | | | | <.001 |
| Yes | 38 (35.85%) | 68 (64.15%) | 106 (69.28%) | |
| No | 0 | 47 (100%) | 47 (30.72%) | |

**Table 3. Comparison of risk factors for pain crises in those with no GF (n = 25)**

| | No GF with pain crises (n = 25) | No GF with no pain crises (n = 567) | Total (n = 592) | *P* value |
|---|---|---|---|---|
| **Age at transplant, y (median)** | 26 | 11 | | <.001 |
| <10 | 2 (0.77%) | 258 (99.23%) | 260 (43.92%) | |
| 11-17 | 7 (4.38%) | 153 (95.63%) | 160 (27.03%) | |
| ≥18 | 16 (9.30%) | 156 (90.70%) | 172 (29.05%) | |
| Weight, kg (median) | 65.0 | 38.0 | | <.001 |
| **KPS** | | | | <.001 |
| <90 | 11 (11.46%) | 85 (88.54%) | 96 (16.44%) | |
| ≥90 | 13 (2.66%) | 475 (97.34%) | 488 (83.56%) | |
| **Donor type** | | | | <.001 |
| HLA identical sibling | 6 (1.89%) | 311 (98.11%) | 317 (53.55%) | |
| HLA mismatched relative | 13 (10.83%) | 107 (89.17%) | 120 (20.27%) | |
| Matched unrelated | 5 (5.38%) | 88 (94.62%) | 93 (15.71%) | |
| Mismatched unrelated | 1 (1.61%) | 61 (98.39%) | 62 (10.47%) | |
| **Graft type** | | | | |
| Bone marrow | 16 (3.88%) | 396 (96.12%) | 412 (69.59%) | .11 |
| Peripheral blood | 8 (7.69%) | 96 (92.31%) | 104 (17.57%) | |
| Umbilical cord blood | 1 (1.32%) | 75 (98.68%) | 76 (12.84%) | |
| **Conditioning intensity** | | | | <.001 |
| Myeloablative | 7 (2.47%) | 276 (97.53%) | 283 (47.80%) | |
| Reduced intensity | 9 (3.73%) | 232 (96.27%) | 241 (40.71%) | |
| Nonmyeloablative | 9 (13.24%) | 59 (86.76%) | 68 (11.49%) | |
| **History of pain crisis 2 y before HCT** | | | | .006 |
| Yes | 22 (6.41%) | 321 (93.59%) | 343 (61.80%) | |
| No | 3 (1.42%) | 209 (98.58%) | 212 (38.20%) | |

logistic regression analyses, we examined the risk associated with pain crisis after HCT for demographic characteristics and patient-related factors before and after HCT. Compared with patients aged ≤10 years, patients with age at HCT of 11 to 17 years (odds ratio [OR], 9.43; 95% CI, 3.20-27.79; $P < .0001$) and age >18 years (OR, 16.62; 95% CI, 5.85-47.16; $P < .0001$) had a higher risk of post-HCT pain crisis. Of 710 patients for whom data on pain crisis were reported in the 2 years before HCT, 450 (63.4%) were reported to have pain crisis in the 2 years before HCT. Patients with a history of pain crisis 2 years before HCT had an increased risk of post-HCT pain crisis (OR, 13.16; 95% CI, 4.08, 42.42; $P < .001$), as well as patients that received HCT from HLA mismatch relative donors (OR, 4.80; 95% CI, 2.48, 9.31; $P < .0001$), unrelated matched donors (OR, 2.71; 95% CI, 1.23-5.97; $P = .0132$), and mismatched unrelated donors (OR, 3.19; 95% CI, 1.44-7.05; $P = .0041$), compared with patients with HLA identical sibling donors. Post-HCT pain crisis was less frequent in patients with a KPS of ≥90 (OR, 0.31; 95% CI, 0.18, 0.55; $P < .0001$). Patients with GF had a higher risk of post-HCT pain crisis (OR, 7.15; 95% CI, 4.20-12.18; $P < .0001$). Among patients who experienced GF, older patients were more likely to experience pain crisis (median age, 21 vs 11 years; $P < .0001$). Avascular necrosis was observed in 35 patients, with an incidence of 4.85% (median, 10 months; range, 0-40 months). No significant relation was found between avascular necrosis and post-HCT pain crisis ($P = .1976$).

Table 5 describes the results of multivariable logistic regression models after using backward Akaike information criterion selection procedures. It describes the estimated ORs of the predictors and the classification performance in the 2 multivariable logistic regression models for predicting the risk of post-HCT pain crisis. In the model without considering the posttransplant factors (Model 1), an increase in age (OR, 1.043; 95% CI, 1.001-1.086; $P = .0401$) and the presence of a history of pain crisis in 2 years before HCT (OR, 6.834; 95% CI, 2.382-28.882; $P = .0018$) increase the risk of pain crisis after HCT. KPS of ≥90 (OR, 0.485; 95% CI, 0.253-0.947; $P = .0310$) decreased the risk of pain crisis after HCT. In another model considering the posttransplant factors (Model 2), the presence of GF (OR, 7.780; 95% CI, 3.974-15.780; $P < .0001$), higher age at HCT (OR, 1.045; 95% CI, 1.004-1.088; $P = .0325$), and the presence of the history of pain crisis in 2 years before HCT (OR, 7.689; 95% CI, 2.547-33.875; $P = .0014$) increase the risk of pain crisis after HCT, whereas a decreased OR of pain crisis after HCT was seen with a KPS of ≥90 (OR, 0.405; 95% CI, 0.199-0.824; $P = .0120$). According to the receiver operating characteristic curves (Figure 2), both models have an area under the curve of >0.85, indicating good classification performance. Nomograms for each model were also presented to describe the relationship between factors and the risk of pain crisis after HCT and to quickly estimate the probability of having pain crisis after HCT (Figures 3 and 4). For example, in Model 1, a patient who is 10 years old, with a weight of 25 kg, has a KPS of

**Table 4. Results of univariable logistic regression for risk factors predictive of pain crises after HCT**

| | Variables | Description | OR (95% CI) | *P* value |
|---|---|---|---|---|
| 1 | Patient age at transplant, y | Unit | 1.08 (1.05, 1.10) | < .0001 |
| 2 | Height before conditioning, cm | Unit | 1.03 (1.02, 1.05) | < .0001 |
| 3 | Weight before conditioning, kg | Unit | 1.03 (1.02, 1.04) | < .0001 |
| 4 | Hb before conditioning | Unit | 0.83 (0.70, 0.99) | .0451 |
| 5 | Number of ACS syndromes within 2 y before HCT | Unit | 1.28 (1.02, 1.61) | .0308 |
| 6 | Patient age (y) group at transplant | 11-17 vs ≤10 | 9.43 (3.20, 27.79) | < .0001 |
| | | ≥18 vs ≤10 | 16.62 (5.85, 47.16) | < .0001 |
| 7 | KPS at HCT | ≥90 vs <90 | 0.31 (0.18, 0.55) | < .0001 |
| 8 | Donor type | HL- mismatched relative vs HLA-identical sibling | 4.80 (2.48, 9.31) | < .0001 |
| | | Matched unrelated donor vs HLA-identical sibling | 2.71 (1.23, 5.97) | .0132 |
| | | Mismatched unrelated donor and cord blood vs HLA-identical sibling | 3.19 (1.44, 7.05) | .0041 |
| 9 | Graft type | Peripheral blood vs bone marrow | 2.43 (1.37, 4.29) | .0022 |
| | | Umbilical cord blood vs bone marrow | 1.23 (0.58, 2.65) | .5899 |
| 10 | Conditioning intensity | Myeloablative vs nonmyeloablative | 0.14 (0.07, 0.27) | < .0001 |
| | | Reduced-intensity conditioning vs nonmyeloablative | 0.25 (0.14, 0.45) | < .0001 |
| 11 | ATG/alemtuzumab given as conditioning regimen/ GVHD prophylaxis | ATG vs none | 0.50 (0.21, 1.15) | .1028 |
| | | Alemtuzumab vs none | 0.35 (0.15, 0.83) | .0170 |
| 12 | Recipient CMV serostatus | Positive vs negative | 1.79 (1.06, 3.01) | .0298 |
| 13 | Year group of transplants | Before 2013 vs after 2018 | 1.14 (0.56, 2.32) | .7117 |
| | | 2013 -2018 vs after 2018 | 0.56 (0.32, 0.99) | .0471 |
| 14 | Received RBC transfusion <30 days before Hb test | Yes vs no | 0.46 (0.27, 0.77) | .0033 |
| 15 | ACS before conditioning | Yes vs no | 2.02 (1.14, 3.58) | .0163 |
| 16 | Transfusion of RBCs for ACS before conditioning | Yes vs no | 4.36 (1.02, 18.56) | .0464 |
| 17 | Sickle nephropathy before conditioning | Yes vs no | 3.28 (1.06, 10.16) | .0400 |
| 18 | Pain crisis requiring hospitalization within 2 y before HCT | Yes vs no | 13.16 (4.08, 42.42) | < .0001 |
| 19 | Frequency of hospitalizations for pain crisis | < 3/y vs ≥ 3/y | 0.45 (0.23, 0.86) | .0167 |
| 20 | GF | Yes vs no | 7.15 (4.20, 12.18) | < .0001 |
| 21 | Acute GVHD, grades 2-4 | Yes vs no | 1.07 (0.59, 1.96) | .8188 |
| 22 | Chronic GVHD | Yes vs no | 0.78 (0.43, 1.42) | .4146 |
| 23 | Avascular necrosis | Yes vs no | 1.91 (0.71, 5.13) | .1976 |

ACS, acute chest syndrome; ATG, anti-thymocyte globulin; CMV, cytomegalovirus; RBC, red blood cell.

<90, a preconditioning Hb level of 7 g/dL, with a history of pain crisis in the 2 years before HCT undergoing a mismatched related bone marrow transplantation with a nonmyeloablative regimen will have a total score of 230 points, indicating a 15% chance of having pain crisis after HCT (Figure 3; supplemental Figure 1). Similarly, in Model 2, if the same patient has GF, the chance of having pain crisis after HCT increases to 34% based on a total score of 259 points (Figure 4; supplemental Figure 2). Supplemental Table 3 and supplemental Figure 3 present the internal validation of the calibration and discrimination of the models using the bootstrap method. Because each model has a large Somers $D_{xy}$ rank correlation value, these 2 models have good predictive ability in discriminating whether a patient will have pain crisis after HCT. Although the slopes of both models are <1, which means a slight underestimated risk for patients at low risk, and a slight overestimated risk for patients at high risk (supplemental Figure 3), the predictions of the overall prevalence of pain crisis after HCT are still calibrated.

## Discussion

In this study on a large cohort of patients with SCD reported to the multicenter CIBMTR, we demonstrate that pain crisis requiring treatment or hospitalization is rare after HCT for SCD in the presence of stable donor engraftment. Furthermore, the study identifies GF, age at HCT, a history of pain crisis in the 2 years before HCT, and donor type as crucial predictors of pain crisis after HCT. We considered the possibility that there might be a correlation between the predictive factors because, intuitively, it would appear that older patients are more likely to have a higher rate of pain crisis before HCT, are more likely to receive HCT from haploidentical or other alternate donors and are more likely to

**Table 5. Results of multivariable logistic regression models after using backward Akaike information criterion selection procedures**

| | Variables | Description | OR (95% CI) | *P* value | Type 3 *P* value |
|---|---|---|---|---|---|
| **Model 1: without post-HCT variable** | | | | | |
| 1 | Patient age at transplant, y | Unit | 1.043 (1.002, 1.086) | .0401 | .0401 |
| 2 | Weight before conditioning, kg | Unit | 1.017 (0.998, 1.035) | .0748 | .0748 |
| 3 | Hb before conditioning | Unit | 0.851 (0.695, 1.042) | .1183 | .1183 |
| 4 | KPS at HCT | ≥ 90 vs < 90 | 0.485 (0.251, 0.936) | .0310 | .0310 |
| 5 | Graft type | Peripheral blood vs bone marrow | 0.976 (0.423, 2.250) | .9538 | |
| | | Umbilical cord blood vs bone marrow | 4.153 (1.642, 10.508) | .0026 | .0097 |
| 6 | Conditioning intensity | Myeloablative vs nonmyeloablative | 0.344 (0.132, 0.897) | .0290 | |
| | | Reduced-intensity conditioning vs nonmyeloablative | 0.729 (0.294, 1.805) | .4944 | .0584 |
| 7 | Pain crisis requiring hospitalization within 2 y before HCT | Yes vs no | 6.834 (2.048, 22.801) | .0018 | .0018 |
| Model 1 area under the curve: 0.863 | | | | | |
| **Model 2: with post-HCT variable** | | | | | |
| 1 | Patient age at transplant, y | Unit | 1.045 (1.004, 1.088) | .0325 | .0325 |
| 2 | Weight before conditioning, kg | Unit | 1.018 (0.998, 1.039) | .0756 | .0756 |
| 3 | KPS at HCT | ≥ 90 vs < 90 | 0.405 (0.200, 0.819) | .0120 | .0120 |
| 4 | Donor type | HLA-mismatched relative vs HLA-identical sibling | 3.407 (1.481, 7.838) | .0039 | |
| | | Matched unrelated donor vs HLA-identical sibling | 2.213 (0.768, 6.376) | .1412 | .0320 |
| | | Mismatched unrelated donor and cord blood vs HLA-identical sibling | 1.032 (0.283, 3.764) | .9620 | |
| 5 | Graft type | Peripheral blood vs bone marrow | 1.354 (0.632, 2.901) | .4351 | |
| | | Umbilical cord blood vs bone marrow | 4.615 (1.119, 19.029) | .0343 | .0998 |
| 6 | Pain crisis requiring hospitalization within 2 y before HCT | Yes vs no | 7.689 (2.193, 26.953) | .0014 | .0014 |
| 7 | GF | Yes vs no | 7.780 (3.917, 15.454) | < .0001 | < .0001 |
| Model 2 area under the curve: 0.899 | | | | | |

experience GF. However, after conducting statistical tests for multicollinearity, we found minimal to no intercorrelation, indicating a minimum correlation between these predictive factors.

Several investigators have investigated the paradox of persistent pain episodes after HCT for SCD. Hsieh et al report that the mean annual hospitalization rate decreased from 3.23 (95% CI, 1.83-4.63) in the year before HCT to 0.63 (95% CI, 0.26-1.01) the first year after, 0.19 (95% CI, 0-0.45) in the second year after, and 0.11 (95% CI, 0.04-0.19) in the third year after transplant.[14] For patients taking long-term narcotics, the mean use per week reduced from 639 mg (95% CI, 220-1058) of intravenous morphine–equivalent

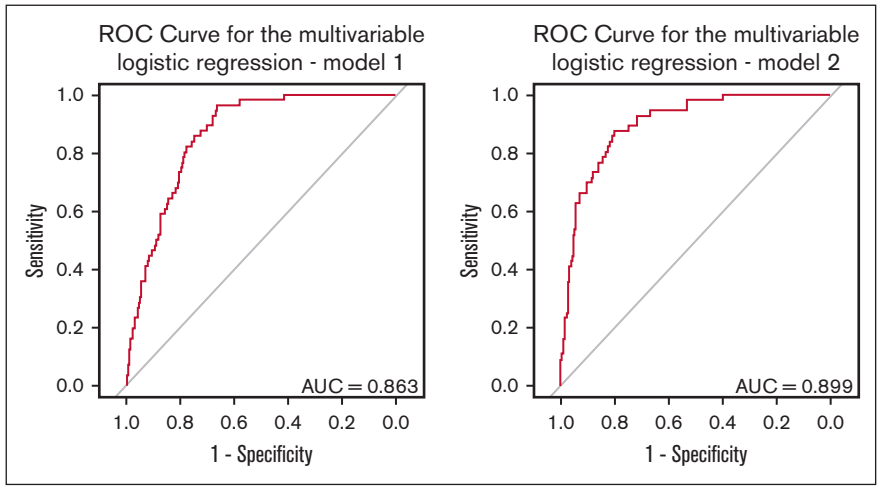


**Figure 2. Predictive performance of models.** Receiver operating characteristic curve of 2 multivariable logistic regression models for predicting the risk of pain crises after HCT, with Model 1 area under the curve (AUC; left): 0.863, and Model 2 AUC (right): 0.899.

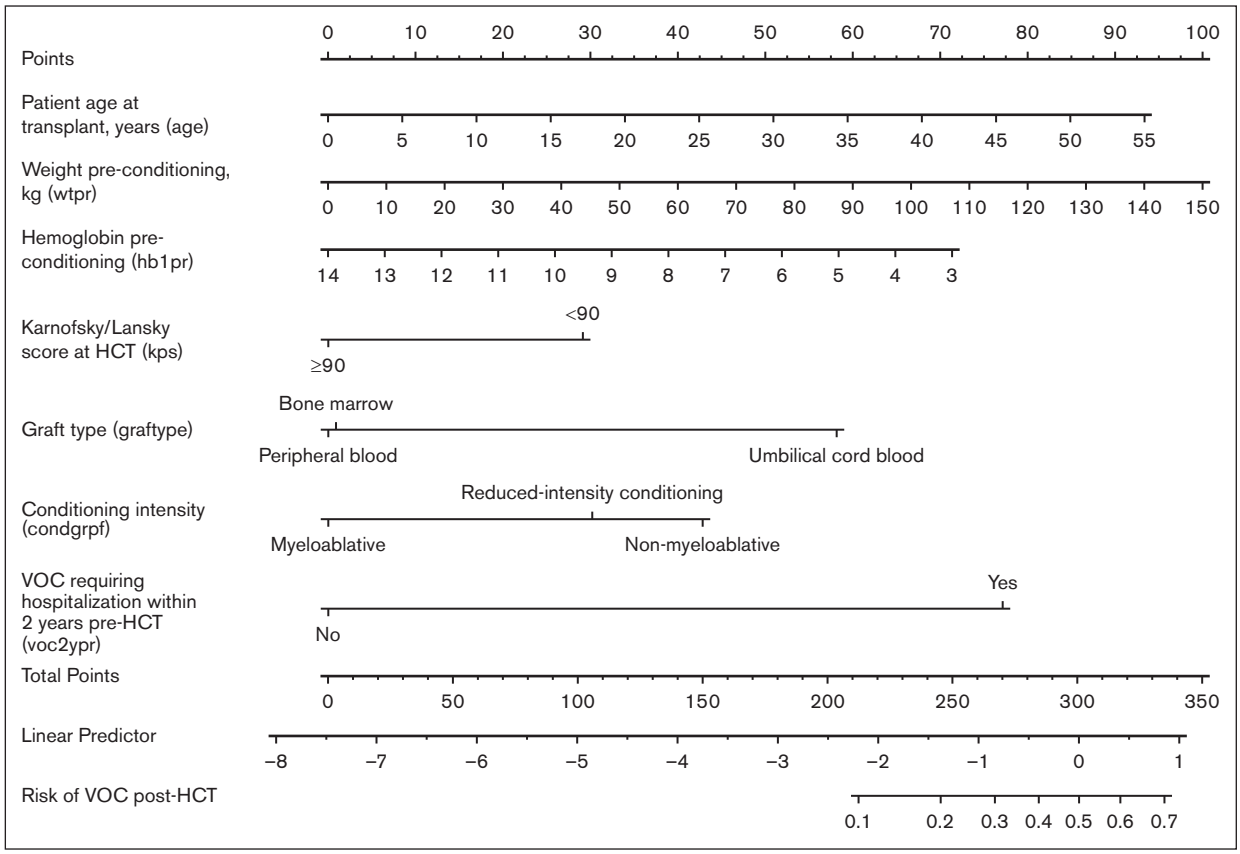


**Figure 3. Nomogram for the multivariable logistic regression Model 1 (without considering post-HCT variable).** Model 1 equation: $\log(\frac{p}{1-p}) = -3.4081 + 0.0423 \times$ age + 0.0166 × wtpr-0.1616 × hb1pr-0.7243 × kps(≥90 vs < 90) − 0.0247 × grafttype_22(peripheral blood vs bone marrow) + 1.4239 × grafttype_23(umbilical cord blood vs bone marrow) − 1.0674 × condgrpf_1(myeloablative vs nonmyeloablative) −0.3161 × condgrpf_2(reduced-intensity conditioning vs nonmyeloablative) + 1.9219 × pain crisis 2ypr(yes vs no), in which "p" represents the probability of having pain crises after HCT).

dose to 140 mg (95% CI, 56-225), 6 months after HCT. All patients who did not have avascular necrosis or structural bone damage were eventually able to discontinue narcotics. Of note, the post-HCT admissions described in their report, however, were not exclusively for the treatment of pain but included pain-related hospitalizations, including arthralgias; myalgias; narcotics withdrawal; hospitalizations for cytomegalovirus and *Clostridium difficile* infection; abdominal events including pain, ulcer, and pancreatitis; and sirolimus-related toxicities such as arthralgia and pneumonitis. Leonard et al used a prespecified definition of VOC as vaso-occlusive pain episode requiring a ≥24-hour hospital or ER observation unit visit or at least 2 visits to a day unit or ER over 72 hours with both visits requiring intravenous treatment, acute chest syndrome, hepatic sequestration, splenic sequestration, or recurrent priapism. They reported a decreased pain crisis rate by 75% in the first year and 99% by 2 years after HCT in patients with engraftment.[15] Intriguingly, they show that even in patients with graft rejection, there is a reduction in pain crises, from 6.6 events (range, 0-24 events) before HCT to 0.5 events, 12 to 24 months after HCT ($P < .001$). Thus, they observed a gradual reduction in pain crises after successful engraftment with the persistence of pain in a small proportion of their cohort of adult patients. Younger patients generally had less VOCs, both at 2 years before ($P = .002$) and 2 years after HSCT ($P = .005$). The difference in VOCs after HCT based on age was eliminated at 12 to 24 months after HCT (not significant). These data indicate the long trajectory of elimination of pain episodes after HCT and the persistence of pain episodes in a small proportion of patients.

Darbari et al collected detailed data on the clinical course, pain, PROMIS quality-of-life measures, opioid use, and laboratory values prospectively before and after HCT. They observed that patients with pain episodes after HCT were more likely to have had chronic pain without contributory SCD complications or the mixed pain phenotype before HCT. They also attribute their findings of persistent pain to the complex neurobiology of pain in SCD, in which different mechanisms may contribute to pain.[16] Interestingly, although none of their patients on short-acting opioids experienced continued pain, use of long-acting opioids was associated with continued pain. They surmise that this difference may reflect more severe disease in this group; or that it also may reflect the contributions from other factors, such as opioid-induced hyperalgesia, central sensitization, or genetic predisposition.[17,18] Taken together, evidence from direct study of patient reported outcomes, as well the use of surrogate markers such as opioid prescriptions, and/or healthcare use, in adult patients after HCT suggests that the frequency of pain episodes gradually diminish over a 2- to 3-year period and that a small minority of patients have persistent pain

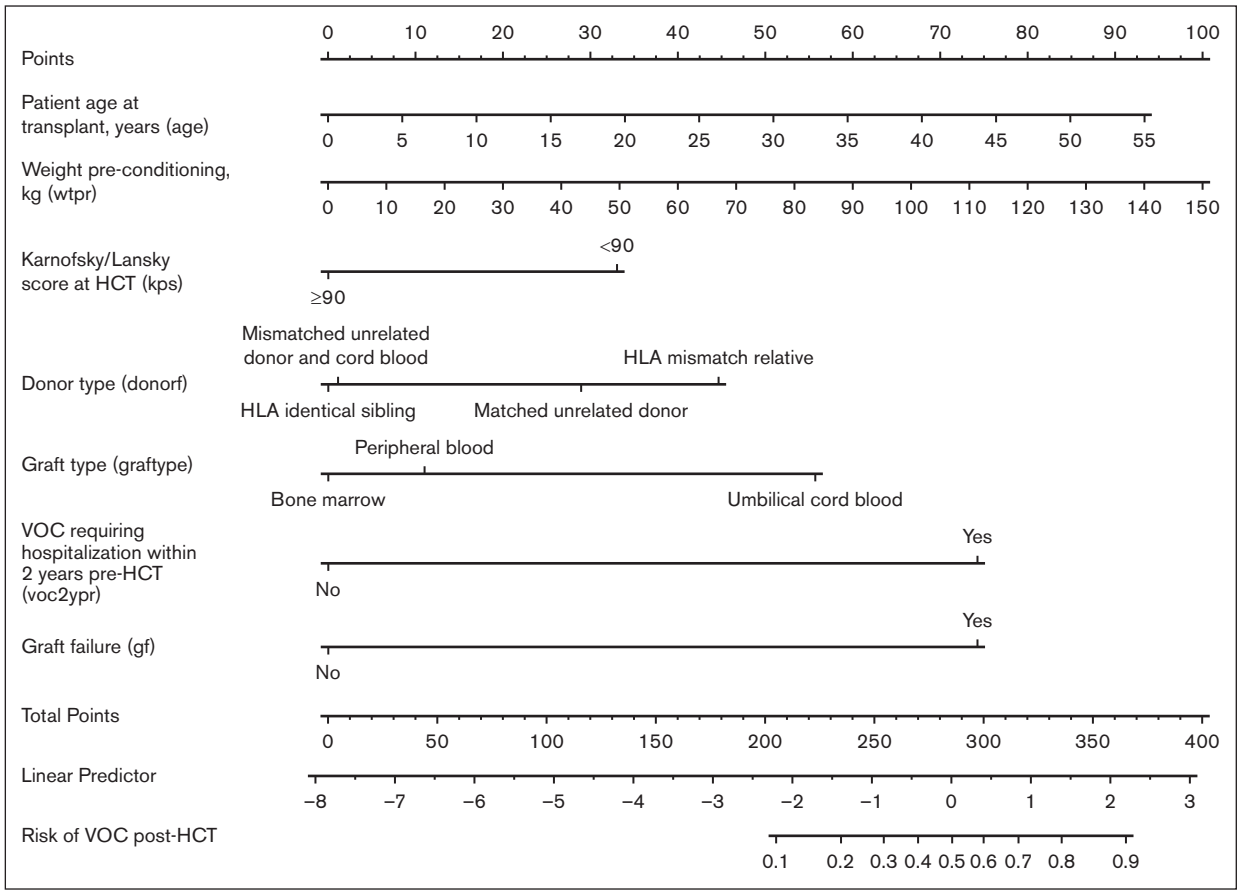


**Figure 4. Nomogram for the multivariable logistic regression Model 2 (considering post-HCT variable).** Model 2 equation: $\log(\frac{p}{1-p}) = -6.9217 + 0.0440 \times \text{age} + 0.0183 \times \text{wtpr} - 0.9050 \times \text{kps}(\geq 90 \text{ vs} < 90) + 1.2258 \times \text{donorf\_3}(\text{HLA-mismatch relative vs HLA-identical sibling}) + 0.7943 \times \text{donorf\_4}(\text{matched unrelated donor vs HLA-identical sibling}) + 0.0315 \times \text{donorf\_5}(\text{mismatched unrelated donor and cord blood vs HLA-identical sibling}) + 0.3033 \times \text{grafttype\_22}(\text{peripheral blood vs bone marrow}) + 1.5294 \times \text{grafttype\_23}(\text{umbilical cord blood vs bone marrow}) + 2.0397 \times \text{pain crisis 2ypr}(\text{yes vs no}) + 2.0516 \times \text{GF}(\text{yes vs no})$, in which "p" represents the probability of having pain crisis after HCT).

despite establishment of donor-derived hematopoiesis. The observation in the single-arm clinical trial reported by Leonard et al of the greater time to recovery from pain crisis after HCT in older patients supports considering HCT earlier during the disease progression. Conversely, a finding of a higher rate of pain crises in older patients with more disease complications will likely inform shared decision making as well as the preparation for pain-focused rehabilitation after HCT. The risk of recurrence of pain crises after HCT is especially relevant in the context of the emerging application of alternate donor allogeneic HCT and autologous gene therapy in older individuals with SCD.

We acknowledge that studies to date have been unable to clearly distinguish these painful episodes as pain crisis or as acute exacerbations of persistent chronic pain after HCT. In this study we report the pain episodes as pain crises, because they were reported as such to the CIBMTR. Furthermore, it is unclear whether the pain episodes in these patients were treated differently after HCT as compared with when they presented with pain crises before HCT. To our knowledge, no qualitative studies have been performed to understand the patient perspective on whether their pain was typical of acute pain crisis. Even such qualitative studies may not distinguish the pain of acute pain crisis from that of acute exacerbation of chronic pain, especially because a high proportion of adults with SCD have mixed-type chronic pain. Therefore, we recommend that it may be best to term these episodes as persistent pain after HCT without characterizing them as VOC but as pain crisis. That some proportion of patients continue to have pain crisis despite successful establishment of donor-derived erythropoiesis and elimination of sickling of red blood cells, suggests that other etiologies of pain in SCD may be contributing and may follow a different trajectory. We recommend that patients with SCD experiencing post-HCT pain crisis receive comprehensive evaluation and multidisciplinary management of their complex pain syndromes. We also recommend that future studies prospectively study the characteristics of pain, its treatment, and outcomes after HCT in granular detail to understand the nature and potential underlying mechanisms.

This study's major strength is that it analyszed all the HCTs performed in the United States for SCD over 3 decades and reported to the CIBMTR. This study demonstrates that the probablilty of patients requiring hospitalization or treatment after HCT is low in those with persistent donor engraftment. It also shows a lower rate of pain crisis in those with GF who underwent HCT at a younger age. Another strength of this study is the development of predictive

nomograms for post-HCT pain crisis based on multivariable logistic regression. The pre-HCT nomogram can be used to guide shared decision making. The post-HCT predictive nomogram, which includes post-HCT events such as GF, provides an overall predictive probability of post-HCT pain crisis. These data thus provide strong support for the efficacy of HCT in relieving severe pain crisis burden, and include vital information to guide shared decision making by patients and physicians. These data also have the potential to generate hypotheses regarding pain and other patient-reported outcomes after HCT, which can be tested in future clinical trials. Such studies are likely to contribute to the discussion of risk–benefit trade-offs, eligibility and exclusion criteria of clinical trials, the cost-effectiveness, and the ethics of therapies for SCD with curative potential.

There are several limitations of this study. We acknowledge the inherent limitations of registry-based studies. Data quality in a registry ultimately depends on the completeness with which data are collected and reported. Of particular concern is the fact that data collection may become difficult once patients are no longer followed-up by their transplant physician, especially if they develop GF. Furthermore, the majority of the patients are children at the time of HCT and are not followed-up for long-term outcomes. Thus, their long-term outcome is unknown. We recognize, therefore, that currently, the utility of the analyses of registry data is limited to generating hypotheses that must be tested in adequately powered prospective clinical trials. For detailed outcome data to become available to the clinician, there is a need to implement consensus guidelines on the critical end points of HCT for SCD, to be collected prospectively. Such data must be collected beofre HCT and continued to be collected after HCT, extending to the long term. These data must also become readily available to the clinician and scientist so as to inform clinical practice and scientific study. Another major limitation is the relatively small number of HCT procedures performed in patients with SCD. Because of the small event rate of pain crisis after HCT, we could not evaluate the predictive model's performance using cross-validation. Validation using an external cohort is needed in future studies to further evaluate and calibrate the model.

Additionally, in this data set of 1718 patients, only 763 were in the CRF track, with data reported on the occurrence of pain crisis. Although the missing data could be a source of bias, the missingness of data was only a function of whether the institution was designated as TED only or CRF institution and whether or not the CIBMTR algorithm assigned an individual patient on the CRF track for CRF completion. Thus, the data may be considered to be missing completely at random. We have, however, not performed any imputation of missing data on the dependent variable, that is, post-HCT pain crisis. We performed, instead, a complete case analysis and acknowledge that the smaller data set may have affected statistical power to detect predictive associations. Another limitation is that data on the frequency of pain crisis or the particular point in time that the pain crisis occurred after HCT is not available in the HCT for SCD data set; hence, the median time to occurrence of pain crisis could not be obtained. It is also impossible to comment whether pain crises are limited to the early period after HCT or if they continue to occur and whether patients are cured long term after HCT. Another limitation is that this study reports pain episodes reported on CIBMTR Form 2130 after HCT as VOC and that there is no option in the form for reporting nonvasocclusive pain episodes. Furthermore, this study reports only on pain crisis requiring hospitalization or treatment. However, most episodes of pain or pain crisis do not result in healthcare use or hospitalization.[19] Also, the HCT for the SCD data set does not capture any details about chronic pain. The SCD preinfusion Form 2030 does not capture chronic pain existing before HCT or whether the chronic pain is associated with any disability. The SCD post-HCT follow-up form 2130 R3.0, modified in July 2021, asks, "Is there a new onset of chronic pain?" Although in the future this question may provide some detail about new onset chronic pain, it does not capture the outcome of chronic pain existing before HCT. We believe that a more detailed capture of the frequency and timing of the instances of pain crisis after HCT and the treatment required would provide critical detail in the registry about this important outcome of HCT for SCD.

Several case series of HCT for SCD also report improvement in quality of life in the short term after HCT.[7,9,11,20,21] Although freedom from pain is an essential outcome of HCT, the overarching goal of HCT is to alleviate disease-related suffering, promote functionality, prevent organ damage, and prolong survival over the long term. The CIBMTR Protocol for the Collection of Patient Reported Outcomes Data may provide more granular detail about pain burden after HCT when patients with SCD after HCT are enrolled in a study. There is also a need to study the relationship of amelioration of pain to functionality, quality of life, organ function, and long-term survival to understand the totality of the impact of HCT on the trajectory of the burden of acute and chronic SCD-related pain.

In conclusion, the recurrence of pain crisis is reported in 8.65% of patients after HCT for SCD. It is correlated with age at HCT, weight, pre-HCT Hb, donor and graft type, conditioning intensity, prior history of pain crisis, and GF. We have generated predictive nomograms for individualized prediction of the risk of pain crisis after HCT, which can be used for shared decision making. These data can inform studies aimed at identifying, preventing, and mitigating the risk of occurrence of pain crisis after HCT for SCD.

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## Authorship

Contribution: L.K. conceived the study, designed and participated in data analysis, and wrote, edited, and finalized the manuscript; Z.H., Y.D., and J.L. performed all analyses, and reviewed, edited, and completed the manuscript; and V.R.N., R.H., A.F., and N.S. reviewed, edited, and finalized the manuscript.

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