Sickle Cell Disease Outcomes in Patients Following Allogeneic Hematopoietic Stem Cell Transplantation – a Systematic Literature Review

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BACKGROUND

- Sickle cell disease (SCD) is a rare genetic disorder characterized by expression of abnormal sickle hemoglobin, which leads to a variety of acute and chronic complications and reduced life expectancy.[1 – 5]
- Vaso-occlusive crisis (VOC) is a hallmark clinical feature of SCD that causes debilitating pain and can lead to additional organ complications and increased mortality.[1 – 3, 6]
- Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is potentially curative for patients with SCD. There has been limited evaluation of the evidence on outcomes after allo-HSCT, particularly disease-specific outcomes such as VOC following allo-HSCT.

OBJECTIVE

- To synthesize evidence from published literature on disease-specific outcomes in patients with SCD following allo-HSCT, using a systematic literature review (SLR) approach.

METHODS

- A comprehensive search was conducted in MEDLINE and Embase to identify English-language publications from interventional and observational studies published from inception of databases up to 12 May 2023, that assessed outcomes in patients with SCD and transfusion-dependent beta-thalassemia (TDT) after allo-HSCT. Relevant conference proceedings were also searched to identify sources from grey literature. Bibliographies of relevant SLRs and meta-analyses were hand-searched to identify eligible studies that were not identified.
- The results presented here focus on a subset of studies that assessed disease-specific outcomes among patients with SCD who underwent allo-HSCT. Specifically, studies that assessed occurrence of VOCs including acute pain, acute chest syndrome (ACS), priapism, and/or splenic sequestration were included. Studies that only reported HSCT-related outcomes were excluded.
  - However, if studies that reported disease-specific outcomes also provided data on graft failure or graft-versus-host disease (GVHD) then these data were also summarized for the review.
- Study selection and data extraction followed the guidance published by the University of York Centre for Reviews and Dissemination (CRD) and reporting of findings followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This review is registered with the International Prospective Register of Systematic Reviews (PROSPERO: CRD42023445828).
- Identified articles were screened by title and abstract as well as full-text by two independent reviewers. Data extraction was performed by a single reviewer and all outcomes were independently verified by a second reviewer. Disagreements between reviewers were resolved by a consensus discussion or a third reviewer.
- Proportions of patients experiencing disease-specific outcomes after allo-HSCT across studies were aggregated and descriptively reported.

RESULTS

Study Screening & Characteristics of Included Studies

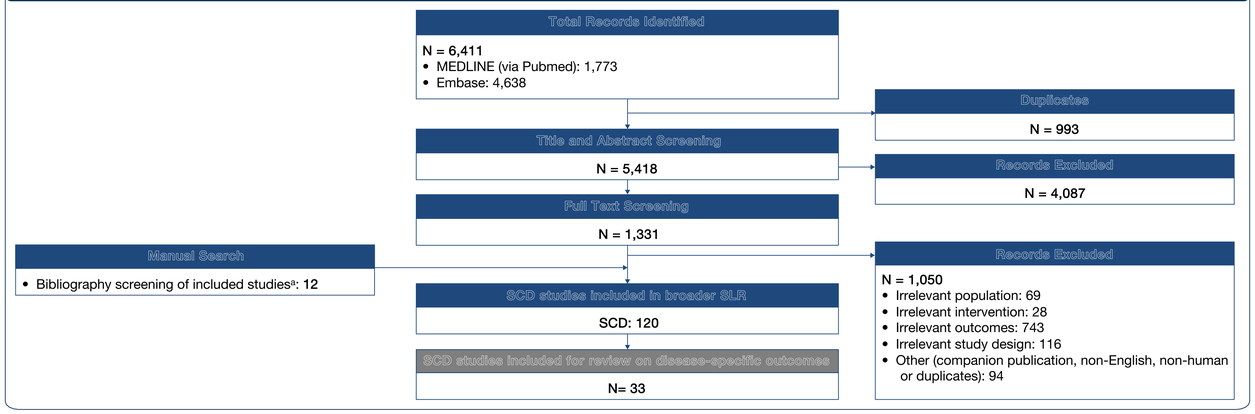
- The broader SLR identified 6,411 records potentially reporting outcomes in patients with SCD and TDT after allo-HSCT. After title/abstract and full-text screening, 120 studies which assessed clinical outcomes after allo-HSCT in patients with SCD were further evaluated. Of these, 33 studies (27.5%) reported on VOCs including acute pain, ACS, priapism, and splenic sequestration (**Figure 1**).
- Most studies included were full-text articles (n = 23 of 33 [69.7%]).
- Most studies included pediatric patients (n = 31 of 33 [93.9%]), HbSS patients (n = 21 of 22 studies that reported genotype [95.5%]), employed myeloablative conditioning regimen (n = 15 of 29 studies that reported conditioning regimen [51.7%]), and included patients treated with matched-sibling donor (n = 25 of 30 studies that reported donor type [83.3%]).
- Most studies were observational by design (n = 24 of 33 [72.7%]) and assessed patients in the United States (n = 19 of 33 [57.6%]). Sample size for included studies varied from 6 to 1,641 patients.

Disease-Specific Outcomes

Vaso-occlusive crises VOCs

- Twenty-eight studies including 3,100 patients assessed occurrence of VOC after allo-HSCT.[7-40]
- VOCs were more frequently assessed as clinical outcomes after allo-HSCT in studies published in 2012 and later. Occurrence of VOC after allo-HSCT was captured in studies with relatively larger sample size (**Figure 2**).
- Terms used to indicate VOC in included studies varied considerably; 10 studies reported as recurrent/refractory VOC, 13 as pain crisis or vaso-occlusive pain crisis, 1 as sickling recurrent events, 3 as vaso-occlusive disease or crisis, 2 as painful vaso-occlusive episode, 1 as painful VOC or ACS, 1 as vaso-occlusive events (VOE) such as pain episode, ACS, hepatic or splenic sequestration, and priapism.
  - Two studies assessed VOC that required hospitalization or emergency room (ER) visit, 2 assessed VOC that occurred despite treatment or not prevented by medical treatment, and 1 assessed VOE that required intervention in medical setting indicated as ≥24-hour hospital or ER visits or ≥2 visits to a day unit or ER over 72 hours with both requiring intravenous treatment or transfusions.
  - Frequency of VOC prior to allo-HSCT was reported in six studies as ≥3 per year (n = 3), ≥2 per year (n = 1), >2 per year for 2 years (n = 1), and multiple VOCs per year (n = 1).
- Eighteen studies (n = 492 patients) reported that all assessed patients were free of events referred to as VOCs after allo-HSCT.

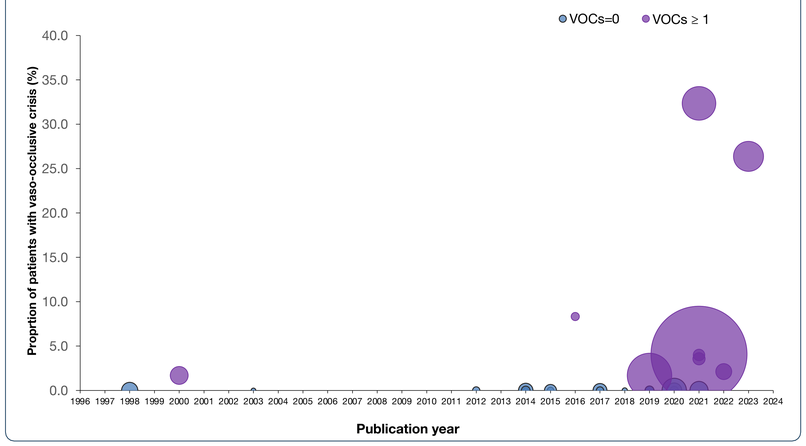
Figure 1. PRISMA Flow Diagram for Selection of SCD Studies



Date of search execution: May 12, 2023.
Abbreviation: allo-HSCT, allogeneic hematopoietic stem cell transplantation; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SCD, sickle cell disease; SLR, systematic literature review; TDT, transfusion-dependent beta-thalassemia.
Note: This SLR focuses on disease-specific outcomes in patients with SCD after allo-HSCT and is part of a broader SLR on outcomes in patients with SCD and TDT after allo-HSCT. The SLR protocol was published in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42023445828).
[a]Reviews and systematic reviews including meta-analyses.

- Nine studies including 2,535 patients reported that a total of 187 (7.4%) patients experienced one or more VOCs after allo-HSCT (range across studies: 1.7%-32.4%; **Figure 2)**. Three of these studies reported occurrence of VOC among engrafted patients after allo-HSCT[10, 12, 32]. Median duration of follow-up for the nine studies varied from 22 months to 144 months.
  - One additional study by Bernaudin et al. 2007, reported 8 of 74 patients (9.2%) experienced one or more composite outcome of VOC or ACS after allo-HSCT.[33]
- Engraftment data was reported for 2,492 patients from 22 studies. Of these, 2,180 patients (87.5%) achieved engraftment after allo-HSCT (range across studies: 71.2%-100.0%).[7-10, 12-15,17-20, 24, 25, 27, 28, 30-36, 38]
- Few studies assessed occurrence of ACS, priapism, or splenic sequestration after allo-HSCT. These results are summarized in **Table 1**.

Figure 2. Proportion of Patients with SCD Experiencing VOC after Allo-HSCT



Abbreviations: HSCT, hematopoietic stem cell transplantation; SCD, sickle cell disease; VOC, vaso-occlusive crisis.
Bubble size reflects sample size across 27 studies that assessed for occurrence of VOCs after allo-HSCT.

Table 1. Proportion of Patients with SCD Experiencing ACS, Priapism, or Splenic Sequestration after Allo-HSCT

Author, year	Sample size	Transplant type & conditioning regimen	Population	Frequency of patients with complication after allo-HSCT	Median follow-up
Acute Chest Syndrome					
Stenger et al, 2019[a]	355	MSD, MAC	Pediatric, adult	4 (1.1%)	50 months
Leonard et al, 2023	163	MRD, MUD, Cord blood MAC, non-MAC	Pediatric, adult	2 (1.2%)	48 months
Priapism					
Stenger et al, 2019*	355	MSD, MAC	Pediatric, adult	1 (0.3%)	50 months
Hsieh et al, 2014	30	MSD, non-MAC	Adolescents, adult	1 (3.3%)	30 months
Splenic Sequestration					
Vermylen et al, 1998	50	MSD, MRD MAC	Pediatric, adult	1 (20%)	60 months

Abbreviations: MAC, myeloablative conditioning; MSD matched sibling donor; MRD, matched related donor; MUD, matched unrelated donor.
[a]Stenger et al., study was conducted using data from Center for International Blood and Marrow Transplant Research (CIBMTR). 66% patients were administered MAC, 59% patients had MSD allo-HSCT.

Transplant-Related Outcomes

- Primary or secondary graft failure was assessed in 25 of 33 studies.[7, 9, 10, 12, 14-23, 25-30, 32-34, 39]
- Acute or chronic GVHD was assessed in 30 of 33 studies.[7, 9, 10, 12-19, 21, 23-30, 32- 34, 39]
- These results are summarized in **Table 2**.

Table 2. Proportion of Patients with SCD Experiencing Graft Failure and GVHD after Allo-HSCT

Outcome	Number of studies that assessed the outcome	Number of studies reporting patients experiencing the outcome after allo-HSCT	Proportion of patients experiencing the outcome,[a] median (range across studies)
Primary graft failure	25	14 (56.0%)	8.2% (1.0% - 18.8%)
Secondary graft failure/ rejection	15	11 (73.3%)	7.7% (1.6% - 83.3%)
Acute GVHD[b]	27	23 (85.2%)	26.7% (2.7% - 50.0%)
Chronic GVHD[b]	26	14 (53.8%)	10.8% (3.6% - 61.5%)

[a]Among studies reporting patients experiencing the outcome after allo-HSCT.
[b]One additional study by Park et al., 2018 reported cumulative incidence of 57.1% (standard deviation [SD] 21.1%) and 47.6% (SD 23.9%) for acute and chronic GVHD respectively, over a maximum 58 months follow-up period after allo-HSCT.[22]

LIMITATIONS

- Limited evidence is published on disease-specific outcomes such as VOC after allo-HSCT in patients with SCD. There is also a lack of chimerism data in patients who continue to experience VOCs which is important to understand disease recurrence.
- Heterogeneity in the definition of VOC precludes presenting pooled estimates using a meta-analysis.
- Possibility of publication bias cannot be ruled out given the lack of full-text publications of some conference abstracts.

CONCLUSIONS

- Based on this systematic literature review, a portion of patients with SCD continue to experience VOCs that require care in a medical setting after allo-HSCT.
- These results highlight the limitations of allo-HSCT for SCD, particularly those related to graft failure, graft rejection, and GVHD.
  - Graft failure could contribute to occurrence of VOC such as acute pain crisis after allo-HSCT

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DISCLOSURES

- **RN**, **NL**, **SI**, **PK**, and **MDB** are employees of Vertex Pharmaceuticals and may own stock/stock options in the company.
- **KL**, **LZ**, and **MD** are consultants of Maple Health Group, LLC.

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