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REVIEW

Clinical Outcomes Among Patients With Sickle Cell Disease and Transfusion-Dependent Beta-Thalassemia Treated With Allogeneic Hematopoietic Stem Cell Transplantation: A Systematic Literature Review

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Background: The purpose of this study is to synthesize evidence on disease-specific outcomes in patients with sickle cell disease (SCD) or transfusion-dependent beta-thalassemia (TDT) following allogeneic hematopoietic stem cell transplant (allo-HSCT).

Methods: A systematic literature review (SLR) was conducted in MEDLINE and Embase to identify publications up to May 2023, including patients with SCD or TDT treated with allo-HSCT. Occurrence of vaso-occlusive crises (VOCs) including acute pain, acute chest syndrome, priapism, and splenic sequestration in SCD, and red blood cell transfusion (RBCT) requirements in TDT were the main outcomes of interest. Transplant-related outcomes such as graft-versus-host disease (GVHD) and graft failure/rejection were summarized in the studies that reported main outcomes. Proportion of patients experiencing VOCs or RBCTs, GVHD, and graft failure/rejection after allo-HSCT were aggregated and descriptively reported with range across studies.

Results: Thirty-one SCD studies met inclusion criteria. Twenty-nine studies assessed for VOC and pain crisis events after allo-HSCT; 11 studies reported ≥1 VOCs after allo-HSCT in 6.9% of the 2,760 patients. Graft failure was reported in 14.4% (0.9%–18.8%, 14 studies) of patients, graft rejection in 5.5% (1.6%–100.0%, 12 studies) of patients, acute GVHD in 22.4% (1.6%–50.0%, 19 studies) of patients, and chronic GVHD in 20.4% (3.3%–57.1%, 14 studies) of patients. Seventy-eight TDT studies met inclusion criteria. Fifty-six studies reported that 8.8% of the 3,107 patients required RBCTs after allo-HSCT. Graft failure was reported in 5.4% (1.1%–80.0%, 21 studies) of patients, graft rejection in 7.5% (0.5%–42.9%, 50 studies) of patients, acute GVHD in 28.4% (5.2%–100.0%, 57 studies) and chronic GVHD in 15.2% (1.3%–50.0%, 51 studies) of TDT patients.

Conclusion: Based on this SLR, after allo-HSCT, a portion of patients with SCD continue to experience VOCs and a portion of patients with TDT continue to require RBCTs, in addition to experiencing GVHD and graft failure or rejection.

Keywords: allogeneic HSCT, sickle cell disease, vaso-occlusive crisis, beta-thalassemia, transfusion dependent

Background

Sickle cell disease (SCD) and beta-thalassemia are among the most common inherited monogenic disorders globally.[1] It is estimated that 5.0%–7.0% of the world's population is a carrier of a significant hemoglobin variant.[2] Despite great progress in the understanding of the pathophysiology of these conditions, the burden of disease remains high as evidenced by the significant morbidity and early mortality in affected patients.[2–4]

SCD is an autosomal recessive disorder caused by a single point variant in the *HBB* gene that encodes the beta-globin, resulting in production of sickle hemoglobin.[5,6] SCD is characterized by recurrent vaso-occlusive crises (VOCs), progressive vasculopathy, and chronic hemolytic anemia which subsequently leads to end-organ damage and early

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mortality.[6–8] VOCs are a hallmark clinical feature of SCD that manifest as debilitating pain and leads to additional organ complications and increased mortality.[9,10] Current treatments for SCD primarily consist of pain management and hydroxyurea which may reduce some acute and chronic complications in some patients.[11,12]

Beta-thalassemia is an autosomal recessive disorder caused by pathogenic variants in the *HBB* gene, resulting in severely reduced or absent production of beta-chains in the adult hemoglobin.[13] Beta-thalassemia is characterized by ineffective erythropoiesis, chronic anemia, and dysregulated iron metabolism.[14,15] Transfusion-dependent beta-thalassemia (TDT) is a severe form of beta-thalassemia which causes severe anemia and organ damage.[16] Patients with TDT require lifelong, regular red blood cell transfusions (RBCTs) to survive, and iron chelation therapy to control iron overload and minimize risk of end-organ toxic effects and damage due to hemosiderosis.[16,17]

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative option for patients with SCD or TDT.[14,18] Prior to receipt of allo-HSCT, nearly every patient with SCD experiences ≥1 VOC annually and up to 2/3rd patients experience ≥3 VOCs per year.[19,20] Patients with TDT were observed to receive a median of 17.4 RBCTs per year and required regular iron chelation therapy prior to allo-HSCT.[21] Average life expectancy for patients with SCD and beta-thalassemia on chronic therapies is observed to be about 40 years and 50 years, respectively, in recent times.[22,23] Eligibility to receive allo-HSCT is limited by the availability of HLA-matched donors and pre-existing comorbidities such as sickling-related or iron-overload-related organ damage among SCD and TDT patients, respectively.[24,25] Recent advances in transplant techniques such as haploidentical donors or use of reduced intensity conditioning expands eligibility for allo-HSCT. Graft-versus-host disease (GVHD), graft rejection, complications associated with immunosuppression such as infections, and transplant-related mortality are some of the known complications of allo-HSCT.[25–29] There is a lack of synthesis of the data on disease-specific outcomes after allo-HSCT in SCD and TDT, whether patients become VOC free or transfusion independent (TI) after allo-HSCT to enable evaluation of the effectiveness of allo-HSCT. Impact on quality of life and functional recovery after allo-HSCT are also important measures in assessing the effectiveness of the transplant, however these factors are beyond the scope of this review.

The primary objective of this systematic literature review (SLR) was to identify published literature on patients with SCD or TDT treated with allo-HSCT and synthesize the occurrence of disease-specific outcomes such as VOCs and RBCT requirements after allo-HSCT, respectively. Additionally, transplant-related outcomes such as GVHD and graft failure/rejection were also summarized to characterize the benefits and limitations of allo-HSCT.

Methods

Literature Search Strategy

This SLR was conducted on clinical outcomes after allogeneic HSCT among patients with SCD and TDT, according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[30,31] This review was registered with the international prospective systematic review register (PROSPERO # CRD42023445828).[32] Please refer to Supplementary Table 1 for the PRISMA 2020 checklist.

A health sciences librarian performed extensive literature searches in MEDLINE (via PubMed) and Embase (via Elsevier) from inception of the databases to May 2023. Only English language human studies were included in the review. No filters were used for any other parameters. Bibliographies of other literature reviews were hand-searched to identify additional eligible studies. Abstracts for major conferences such as American Society of Hematology (ASH), Tandem Meetings (the American Society for Transplantation and Cellular Therapy [ASTCT] and the Center for International Blood and Marrow Transplant Research [CIBMTR]), European Hematology Association (EHA), European Society for Blood and Marrow Transplantation (EBMT) that were indexed in MEDLINE were also included in the review. Search strategy was developed by researching appropriate subject headings (ie, MeSH, Emtree terms) and free search terms and are available in Supplementary Table 2. The strategy was validated by comparing search results to a sample set of published studies and review papers that were expected to be identified for this literature review.

Study Selection Criteria

Citations identified in the database searches were exported to an EndNote library, where duplicate citations were identified and removed. Citations were then exported to a literature review screening platform called DistillerSR®,

which was used for all phases of the study selection process.[33] Each citation was evaluated against the predetermined inclusion criteria in two screening phases.

Inclusion and exclusion criteria were established a priori. English language studies with patients with SCD or beta-thalassemia of all ages treated with allo-HSCT were eligible to be screened for inclusion. Studies that reported data on at least one of the pre-determined clinical outcomes after allo-HSCT were eligible for full text screening. There was no restriction applied by donor type, stem cell source, conditioning regimen, study design, or geographical location, but studies reporting data on <5 patients were excluded. Commentaries, letters, notes, editorials, pre-clinical studies, and expert opinion were excluded. Previously published SLRs were included only for bibliography check purposes.

Each title and abstract were independently reviewed against the eligibility criteria by two reviewers. Citations proceeded to full-text review if at least one disease-specific SCD or TDT outcome was reported; citations reporting only allo-HSCT-related outcomes were excluded. In cases where the applicability of the inclusion criteria to the title/abstract was unclear and/or the abstract was not available for review, the citations were included to ensure that all potentially relevant studies are captured. Each full-text publication was independently reviewed against the eligibility criteria by two reviewers. Citations were included if at least one disease-related clinical outcome was reported and were excluded if only transplant-related outcomes were reported. Studies providing insufficient information for the evaluation of the eligibility criteria were excluded at this stage to ensure that only relevant publications are captured. The number of publications excluded during the full-text review phase along with their respective primary reason for exclusion was recorded and presented in a PRISMA diagram in Figure 1. For both screening phases, any disagreements between the two reviewers regarding the eligibility of a study were discussed until a consensus was met. No unresolved conflicts required a third reviewer.

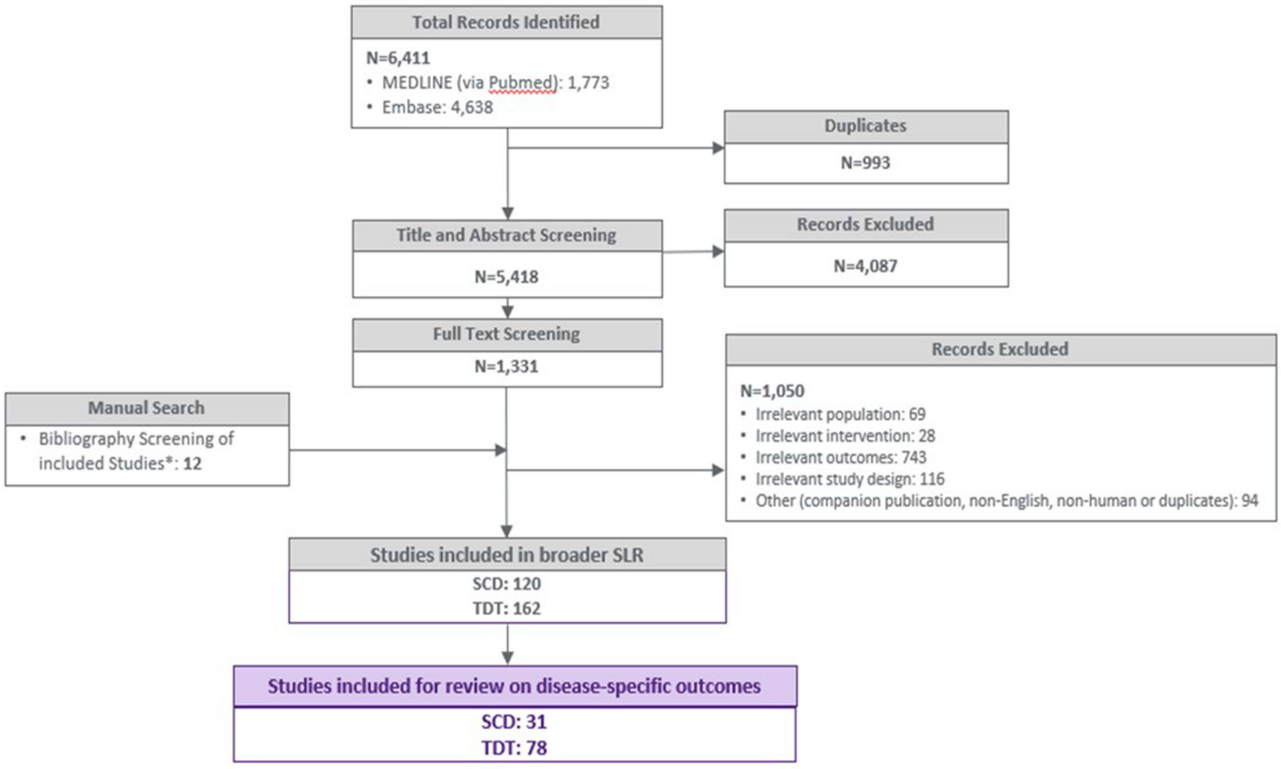

Figure 1 PRISMA flow diagram for selection of sickle cell disease (SCD) and transfusion-dependent beta-thalassemia (TDT) studies for SLR.
Note: Date of search execution was May 12, 2023.
Abbreviations: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SCD, sickle cell disease; SLR, systematic literature review; TDT, transfusion-dependent beta-thalassemia.

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Data Extraction

Data extraction was performed by a single individual for each included study and 100.0% of the outcomes were independently verified by a second reviewer once completed. Any discrepancies or missing information identified by the second reviewer were discussed by both reviewers until a consensus was reached. Unresolved conflicts were decided by a third reviewer. If multiple publications reported the same outcomes from the same study cohort, then full-text publications were prioritized over conference abstracts; if multiple abstracts were published then the latest abstract was prioritized; and larger sample size publication using the same cohort was prioritized over smaller sample size publication. If multiple publications reported different outcomes from the same study cohort, then only the publication that met a greater number of inclusion criteria was used for data extraction.

Data were extracted into an Excel workbook developed and validated for this review. Pre-determined disease-related outcomes, such as occurrence of VOC including pain crisis, acute chest syndrome (ACS), priapism, and splenic sequestration in SCD, transfusion independence in TDT, and transplant-related outcomes such as graft failure/rejection and GVHD for both SCD and TDT, were extracted as available in each included study. For this synthesis, primary graft failure or graft failure events were reported as graft failure, and secondary graft failure or graft rejection events were harmonized to report as graft rejection. Only disease- and transplant-related outcomes after first allo-HSCT were synthesized from SCD and TDT studies included in this review. Additional key elements such as study, population, and transplant characteristics were also extracted.

Data Syntheses

Key results of this SLR were synthesized following the reporting standards outlined in the expanded 2020 PRISMA checklist and presented by disease type (SCD or TDT). Outcomes reported as transfusion independence (TI) and transfusion dependence (TD) were harmonized to report proportion of patients achieving TI after allo-HSCT for all included TDT studies. Proportion was calculated for each outcome by pooling results across studies and dividing the number of patients with the outcome by the total number of patients. Additionally, for each outcome, the proportion of patients experiencing the outcome in each study was also calculated. Results for each outcome was reported in this SLR as the proportion from all studies, and the median proportion with range across proportions calculated for each study. The median and range for proportions considers the variability in sample size across studies. Studies reporting zero frequency for a given outcome were summarized in the review but not included in calculation of proportions. A meta-analysis was not planned for this review due to potential for small number of studies and heterogeneous study characteristics and definitions, such as study population and definition of outcomes. Synthesized results for proportion of patients with SCD who experienced VOC and proportion of patients with TDT who became transfusion independent after allo-HSCT were presented as bubble plots to illustrate the temporal distribution of outcomes.

Assessment of Study Quality

The Newcastle Ottawa Scale (NOS) for cohort and case-control studies,[34] and the National Institutes of Health (NIH) quality assessment tools for pre-post studies without control group, case series, and cross-sectional studies[35] were used to assess the risk of bias in included studies. Only studies published as full-text articles were subject to quality appraisal. Quality assessment was performed by one reviewer and about 10.0% of these assessments were verified by a second reviewer. Discrepancy between reviewers was resolved by achieving consensus or by a third reviewer.

Results

A comprehensive literature search for the review identified 5,418 non-duplicate full-text articles and abstracts on SCD and TDT treated with allo-HSCT, in MEDLINE and Embase. After title and abstract screening, 1,331 SCD and TDT publications were eligible for full-text screening. Among the full-text screened publications, 120 SCD and 162 TDT publications reported data on clinical outcomes and were included in the review. Results presented here are a focused synthesis of evidence on disease-related outcomes: SCD (VOCs including acute pain crisis, ACS, priapism, splenic sequestration) and TDT (transfusion independence). Thirty-one unique SCD publications (1997–2023) and 78 unique

TDT publications (1986–2023) were synthesized to report results on occurrence of disease-specific and transplant-related outcomes after allo-HSCT (Figure 1 and Supplementary Tables 3 and 4).

Sickle Cell Disease (SCD)

Study Characteristics

The majority of 31 SCD publications included pediatric patients (n = 31, 100.0%),[36–65] patients with HbSS genotype (n=18 of 19 studies that reported genotype, 94.7%),[37–39,42,44,45,47,49–51,54,56–58,60,62,63,66] and patients underwent HLA-matched sibling donor (MSD) HSCT (n = 22 of 29 studies that reported donor type, 75.9%).[37,40–47,49,51,52,54–61,63–65] Thirteen of the 29 (44.8%) studies included patients treated with myeloablative conditioning.[37,40,41,46,47,49,55,56,60–64] Twenty-five of the 31 studies reported engraftment data on a total of 2,534 patients.[36–40,42–49,51,54–60,62,63,65,66] Most were non-interventional studies by design (n = 24 of 31, 77.4%),[36,37,40–52,54–57,61–65] sample sizes varied from 6 to 1,641 patients, more than half included patients from the United States (n = 16 of 31, 51.6%)[38,39,41,44,45,48–50,53,56–61,64,66] and about one-third studies included patients from Europe (n = 11 of 31, 35.5%).[37,40,43,46,47,51,62–66]

VOCs After Allo-HSCT

Acute Pain

Twenty-nine SCD studies assessed occurrence of events referred to as VOC after allo-HSCT among a total of 3,181 patients.[37–55,57,58,60–67] Terms used to indicate VOC varied considerably among included studies: 11 studies reported as recurrent/refractory/frequent/multiple VOC,[38,42,44,46,51,52,58,60,62,64,65] 8 as pain crisis or vaso-occlusive pain crisis,[39,41,43,45,47,61,63,66] 1 as sickling recurrent events,[42] 3 as vaso-occlusive disease or crisis,[40,48,55] 1 as painful VOC or ACS,[46] and 1 as vaso-occlusive events (VOEs) that included acute pain episode, ACS, hepatic or splenic sequestration, and priapism.[49] Of the 29 studies, 2 assessed VOC that required hospitalization or emergency room (ER) visit,[49,50] 2 assessed VOC that occurred despite hydroxyurea treatment or were not prevented by medical treatment,[51,54] and 1 assessed VOE that required intervention in medical setting indicated as ≥24 hour hospital stay, or at least 2 visits to a day unit or ER over 72 hours with both requiring intravenous treatment.[49] Six studies included frequency in their terms to indicate VOCs prior to allo-HSCT: ≥3 per year (n = 3),[53,54,59] ≥2 per year (n = 1),[36] >2 per year for 2 years (n = 1),[66] and multiple VOCs per year (n = 1).[58] VOC occurrence after allo-HSCT was more frequently assessed as clinical outcomes in studies published after 2012 and was captured in studies with relatively larger sample sizes (Figure 2). Twenty-two of the 29 studies included patients with SCD,[38–43,45–52,55,57,59–63,65] and 7 studies included patients with severe or high-risk SCD.[37,44,53,54,58,64,66]

One hundred ninety-one (6.9%) of 2,760 patients had ≥1 VOCs during follow-up after allo-HSCT as reported in 11 studies (Across studies: median: 4.0%, range: 0.4%–32.4%).[37,40,41,47–50,58,61,64,66] (Figure 2) Of the 25 studies that reported engraftment data in 2,534 patients in the overall SLR, 2,169 patients (85.6%) achieved neutrophil and/or platelet engraftment after allo-HSCT (range - 81.3%–100.0%; one study reported engraftment in 64.7% patients[39]). Three of these studies reported occurrence of VOC among patients with stable engraftment after allo-HSCT.[48,49,58] Median duration of follow-up for studies that reported ≥1 VOCs after allo-HSCT ranged from 17 months to 95 months.

Eighteen of the 29 studies assessed for VOCs reported that none of the 421 SCD patients experienced any VOC after allo-HSCT with a median duration of follow-up ranging from 19 months to 60 months.[38,39,42–46,51–55,57,59,60,62,63,65]

Acute Chest Syndrome, Priapism, Splenic Sequestration

SCD studies reported occurrence of ACS or priapism after allo-HSCT; ACS (n = 3 studies; 640 patients),[36,49,61] or priapism (n = 2 studies; 385 patients) (Table 1).[44,61] None of the studies reported occurrence of splenic sequestration after allo-HSCT. Occurrence of ACS or priapism was relatively lower compared to acute pain VOCs after allo-HSCT. ACS was reported in 0.82% after graft failure,[36] 1.1% with unknown graft status,[61] and 1.2% after graft rejection[49] of patients after allo-HSCT at a median follow-up of 48 months, 50 months and 24 months, respectively. Priapism was reported in 0.3%[61] and 3.3%[44] patients after allo-HSCT at a median follow-up of 50 months and 41 months, respectively.

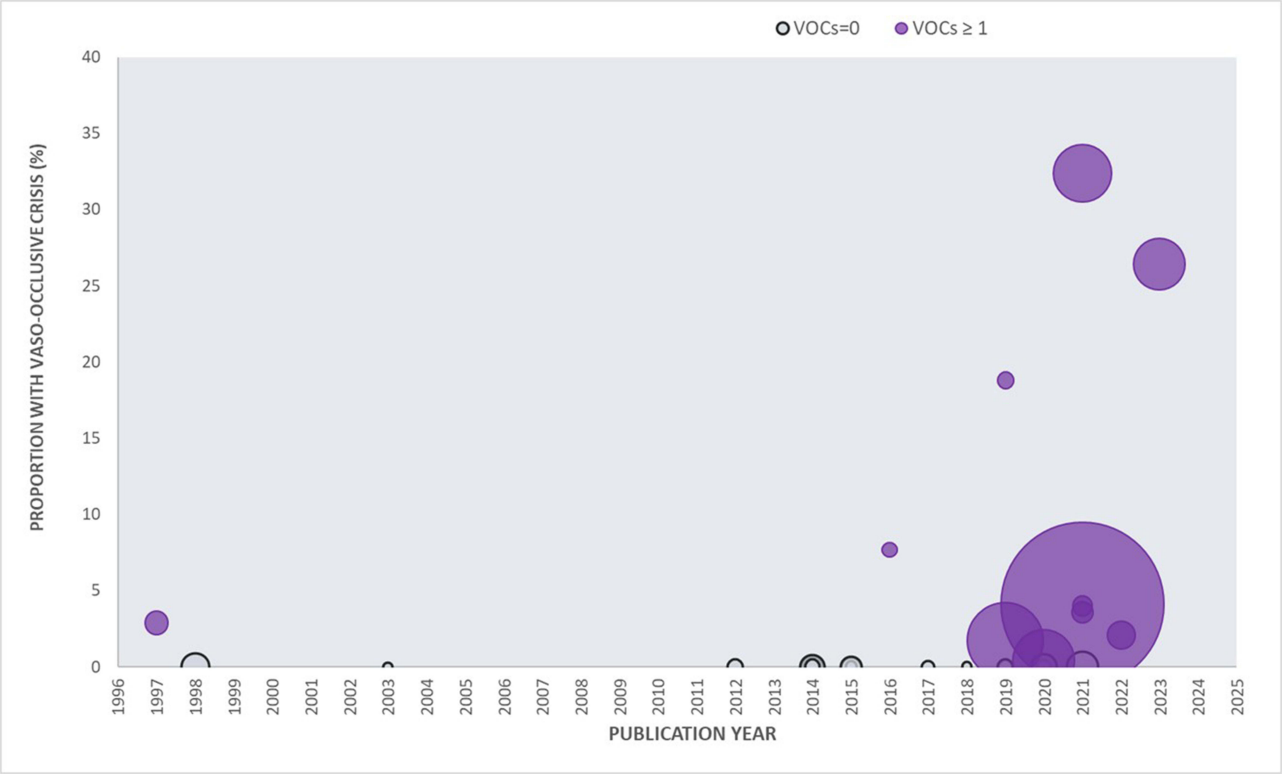

Figure 2 Roportion of vaso-occlusive crisis (VOC) reported in studies among patients with SCD after allogeneic HSCT.
Abbreviations: HSCT, hematopoietic stem cell transplant; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

Transfusion-Dependent Beta-Thalassemia (TDT)

Study Characteristics

The majority of TDT studies included pediatric patients (n = 75 of 76 studies that reported age, 98.6%),[21,25,38,55,67–137] assessed patients treated with MSD HSCT (n=44 of 74 studies that reported donor type, 59.5%),[21,55,69,70,72,74–81,83–86,89,90,93,94,98,101–103,105,107–111,113,115–121,124,131,133,134,138–140] and myeloablative conditioning (n = 46 of 72 studies that reported conditioning

Table 1 Proportion of Patients With SCD Experiencing Acute Chest Syndrome and Priapism, After Allogeneic HSCT

Author, Year	Sample Size	Transplant Type and Conditioning Regimen	Population	Frequency of Patients with Complication After Allo-HSCT	Median Follow-Up
Acute Chest Syndrome					
Alzahrani et al, 2021[36]	122	MRD, non-MAC	Pediatric, adult	1 (0.82%)	48 months
Stenger et al, 2019[61]*	355	MSD, MAC	Pediatric, adult	4 (1.1%)	50 months
Leonard et al, 2023[49]	163	MRD, MUD, Cord blood MAC, non-MAC	Pediatric, adult	2 (1.2%)	24 months
Priapism					
Stenger et al, 2019[61]*	355	MSD, MAC	Pediatric, adult	1 (0.3%)	50 months
Hsieh et al, 2014[44]	30	MSD, non-MAC	Adolescents, adult	1 (3.3%)	41 months

Note: *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.
Abbreviations: HSCT, hematopoietic stem cell transplant; MAC, myeloablative conditioning; MSD, matched sibling donor; MRD, matched related donor; MUD, matched unrelated donor.

regimen, 63.9%).[70–72,75,77–84,88–93,96,98–102,104,105,107,108,110,111,116,117,120,122,124,126–128,131,132,134,135,138,139] Forty-seven of the 78 included studies reported on patients with thalassemia-major,[25,55,69–71,73,74,78,81–84,86,87,91–93,95–98,100,102,104–106,110–117,119,120,128–130,132,133,135,137,141] 28 reported on patients with TDT,[21,67,72,76,77,79,80,85,88,89,94,99,101,103,107,109,118,121–126,131,134,139,140,142] and 3 reported on patients with beta-thalassemia.[75,108,127] Most were non-interventional studies by design (n = 73 of 78, 93.6%)[21,55,68–72,74–80,82–116,118–135,137–141] and had sample sizes varying from 5 to 328 patients. The top three countries from 78 studies were China (n = 15, 19.2%),[25,76,77,79,80,95,106,122,124,128,129,133,135,137,139] Italy (n = 13, 16.7%),[21,68,73,75,86,98,104,108,111,113,120,126,131] and India (n = 7, 8.9%).[67,78,82,87,109,112,118]

Transfusion Outcomes After Allo-HSCT

Seventy-eight studies assessed and reported RBCT requirements at the end of the study follow-up period after allo-HSCT. Fifty-five studies assessed transfusion independence (TI),[25,38,55,67,69,71,73,74,76–81,86–88,90–93,95–104,106,109,112–119,121,123,124,126–129,132–134,137,139,141,142] 20 studies assessed transfusion dependence (TD),[21,68,70,72,75,82–85,89,94,105,107,108,120,122,125,131,135,140] and 3 studies assessed both.[110,111,130] TI was most frequently reported as absence of regular RBCTs and TD was reported as dependence on RBCTs. Only 4 studies reported the duration of RBCT-free period to be classified as TI. Two studies defined this duration as at least 1 year after allo-HSCT,[91,92] one study defined this duration as no RBCTs starting 2 months after allo-HSCT,[129] and one other study defined the duration as absence of RBCTs after engraftment.[116]

Studies included in this review assessed transfusion outcomes in a total of 3,848 patients. A total of 3,784 patients (98.3%) achieved neutrophil and/or platelet engraftment after allo-HSCT. Twenty-one patients (0.6%) died before engraftment. Among engrafted patients, 3,445 (91.1%) patients were alive and TI after allo-HSCT (Across studies: median proportion - 86.6%; range - 20.0%–99.5%) (Figure 3). Fifty-six studies reported that 8.8% patients with graft failure resumed regular RBCTs after allo-HSCT. Median duration of follow-up after allo-HSCT was 6 months to 288 months. A sensitivity analysis excluding studies with <6 months of minimum follow-up after allo-HSCT showed similar TI rates as for overall analysis.[25,75,76,80,81,88,95,102,106,107,109,112,119,125,128,131,134,140] This approach was implemented to account for the possibility of biased classification of patients with RBCT support immediately after allo-HSCT, as transfusion dependent.

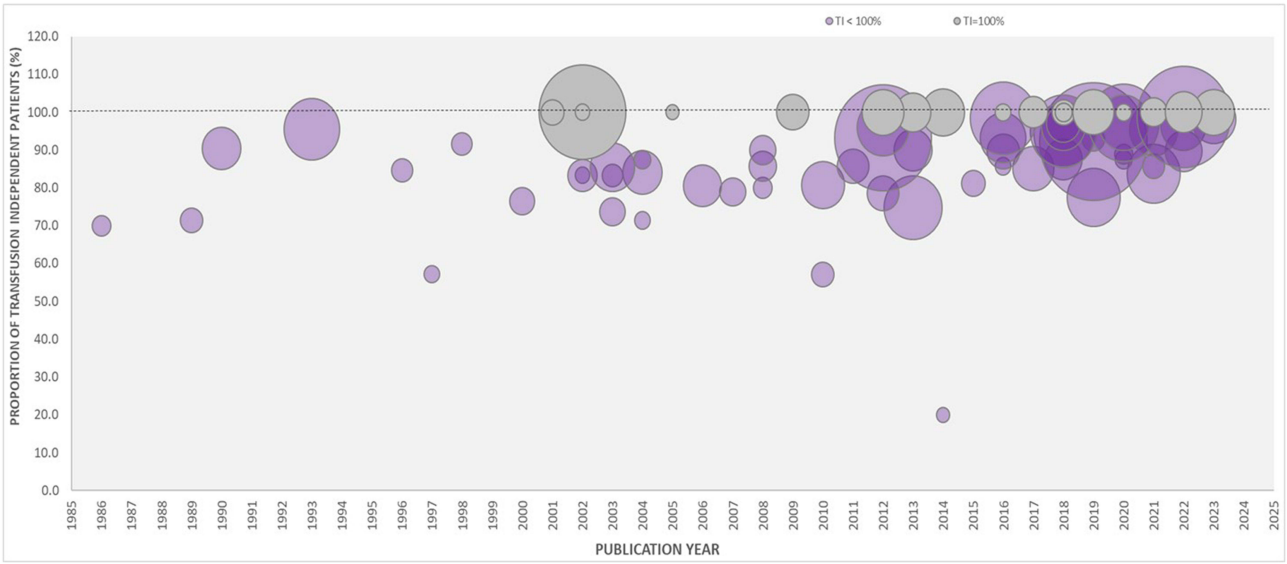

Figure 3 Proportion of transfusion independence reported at end of the study follow-up period among patients with TDT after allogeneic HSCT.
Abbreviations: HSCT, hematopoietic stem cell transplant; TDT, transfusion-dependent beta-thalassemia; TI, transfusion independence.

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Transplant-Related Outcomes

SCD

Graft failure or graft rejection were assessed in 27 of the 31 studies (Table 2)[36–40,42–49,51,53–60,62–66] Fourteen studies reported graft failure in 14.4% patients (Across studies: median: 9.5%; range: 0.9%–18.8%).[36,38,39,44,45,47–49,56,59,62,64,66,143] Twelve studies reported graft rejection in 5.5% patients (Across studies: median: 6.9%; range: 1.6%–100.0%).[36,39,40,45,47,53,57–60,63,143]

Acute or chronic GVHD was assessed in 27 of the 31 included studies (Table 2).[36,37,39,40,42,43,45–49,51–54,56–66] Acute GVHD events occurred in 22.4% patients as reported in 19 studies (Across studies: median: 27.3%; range: 1.6%–50.0%).[36,37,39,40,43,45,46,49,51–54,56,59,60,63–66] Fourteen studies reported chronic GVHD events in 20.4% patients (Across studies: median: 10.7%; range: 3.3%–57.1%).[46,48,49,52–54,56,61–66,143]

TDT

Graft failure or graft rejection were assessed in 58 of the 78 studies (Table 2).[21,38,55,67,69–75,77–79,81,83,84,86,87,89–91,94,96,97,99,102–110,112–120,122–124,126,129–131,133–135,137,140–142] Twenty-one studies reported graft failure events in 5.4% patients (Across studies: median – 8.4%; range - 1.1%–80.0%).[21,67,74,77,79,81–86,99,102,104,106–108,116,119,124,142] Fifty studies reported graft rejection in 7.5% patients (Across studies: median – 10.0%; range - 0.5%–42.9%).[21,69–73,75,76,78–81,83–87,89,90,94,96,97,99,102,104–111,115,117–120,122–126,130,131,133,135,138–141]

Acute or chronic GVHDs were assessed in 66 of the 78 studies (Table 2).[21,55,67,70–82,84,86,88,89,91–93,95–113,115–124,126–129,131–135,137,139,140,142] Fifty-seven studies reported acute GVHD in 28.4% patients (Across studies: median – 26.3%; range - 5.2%–100.0%).[21,55,67,70–76,78–81,84,88,89,91–93,95–106,108–113,115–119,121–124,128,129,132–135,137,139,140,142] Fifty-one studies reported chronic GVHD in 15.2% patients (Across studies: median – 16.4%; range - 1.3%–50.0%).[21,67,70,72–80,82,84,86,89,92,93,95–99,101–105,107–109,111,113,116–120,122,123,127–129,131–135,137,140,142]

Table 2 Proportion of Patients With SCD or TDT Experiencing Graft Failure and Graft-Versus-Host Disease After Allogeneic 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[#]	Study-Level Proportion of Patients Experiencing the Outcome, Median (Range)[#*]
Sickle Cell Disease				
Graft failure	24	14 (58.3%)	14.4%	9.5% (0.9% - 18.8%)
Graft rejection	16	12 (75.0%)	5.5%	6.9% (1.6% - 100.0%)
Acute GVHD	26	19 (73.1%)	22.4%	27.3% (1.6% - 50.0%)
Chronic GVHD	24	14 (58.3%)	20.4%	10.7% (3.3% - 57.1%)
Transfusion-Dependent Beta-Thalassemia				
Graft failure	78	21 (26.9%)	5.4%	8.4% (1.1% - 80.0%)
Graft rejection	78	50 (64.1%)	7.5%	10.0% (0.5% - 42.9%)
Acute GVHD	61	57 (93.4%)	28.4%	26.3% (5.2% - 100.0%)
Chronic GVHD	60	51 (85.0%)	15.2%	16.4% (1.3% - 50.0%)

Notes: [#]Among studies reporting patients experiencing the outcome after allo-HSCT. *Data is presented as median proportion and range of proportion across studies.

Abbreviations: GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplant; SCD, sickle cell disease; TDT, transfusion-dependent beta-thalassemia.

Risk of Bias Assessment

Twenty SCD studies and 55 TDT studies were assessed for risk of bias using validated and reliable tools for study quality assessment.[25,36,38,39,42,45,47–51,53,55–60,62,63,65–71,73–81,83,84,86,89–95,97,99–101,105,107–112,115–120,123–132,134,140] Key sources of bias in assessed studies were likely to stem from incomparability between cohorts/cases and controls, as well as issues with reporting of patient follow-up. Several studies did not control for important confounding factors, such as age resulting in study groups that were often incomparable. Another source of uncertainty was related to patient follow-up as there was lack of description of patients lost to follow-up and rationale for choice of follow-up period to assess for disease outcomes.

Discussion

We performed a systematic literature review to synthesize evidence on occurrence of VOCs and RBCT requirements following allo-HSCT in patients with SCD or TDT, respectively. Overall, 6.9% of patients with SCD continue to experience VOCs after allo-HSCT and 8.8% of patients with TDT continue to require regular RBCTs beyond the anticipated transfusion support after allo-HSCT, based on an unadjusted analysis of the included studies. SCD and TDT studies included in this SLR also reported considerable burden due to graft failure, graft rejection, and acute and chronic GVHD after allo-HSCT. Taken together these data provide important context for clinicians when considering allo-HSCT as a treatment option. These results could serve as a rationale for future research to identify patients with SCD who experienced chronic pain prior to their allo-HSCT and are at risk to continue to have chronic pain or acute exacerbations of their chronic pain after allo-HSCT, or patients with TDT who will be at risk for graft failure/rejection and will resume regular transfusions after allo-HSCT. Such findings are likely to inform treatment and management options for patients after allo-HSCT.

To our knowledge, this represents the first SLR on disease-related outcomes in patients with SCD or TDT after allo-HSCT that includes results from both clinical trials and real-world studies; previously published Cochrane reviews on allo-HSCT outcomes in SCD and TDT focused only on clinical trials.[144,145] A study by Krishnamurti et al using data from the Center for International Blood and Marrow Transplant Research (CIBMTR) registry observed recurrence of pain crisis requiring hospitalization or treatment in 8.7% of SCD patients after allo-HSCT.[146] Prior history of VOC, older age, graft failure, and donor types were noted as important predictors for recurrence of pain crisis following successful allo-HSCT. Studies reporting acute pain events after allo-HSCT indicate the possibility of other etiologies of pain in these patients such as chronic pain due to avascular necrosis of a joint or leg ulcers, neuropathic pain or chronic pain without evident pathology.[146,147] Another study by Leonard et al, that was included in this SLR, reported that the mean rate of VOE post allo-HSCT was lower in engrafted patients (0–12 months after allo-HSCT: 0.8 per 100-patient years; 12–24 months after allo-HSCT: 0.1 per 100-patient years) compared to those patients with graft rejection (0–12 months after allo-HSCT: 1.1 per 100-patient years; 12–24 months after allo-HSCT: 0.8 per 100-patient years).[49] Results from the above mentioned studies indicate that patients with SCD who have risk factors such as older age at the time of allo-HSCT, higher pain burden before allo-HSCT, or do not have stable donor engraftment after allo-HSCT could be at higher risk for continued experience of VOCs or pain crisis. Additional studies will be needed to understand the complex etiology of pain events in patients with SCD following allo-HSCT.

Similarly, TDT studies included in this SLR noted that graft failure or graft rejection resulted in thalassemia recurrence and patients resuming regular RBCTs after allo-HSCT. This SLR noted that patients with TDT who had sustained engraftment remained transfusion free, including those with stable mixed chimerism. Two studies reported RBCTs among engrafted patients however these patients subsequently became transfusion independent.[21,107] Lin et al, reported that 1 patient received one RBCT after allo-HSCT for transient anemia. Merli et al, reported that 7 patients needed RBCT for 3–12 months after allo-HSCT - 2 patients for thalassemia and 5 patients for other reasons including gastrointestinal bleeding. Studies that reported RBCT requirements due to graft failure or graft rejection in patients following allo-HSCT speculated that older age, higher RBCT burden pre-allo-HSCT, higher Pesaro risk score (particularly group III who are patients at higher risk for graft rejection), alloimmunization due to prior RBCTs, and disease-related immunocompromised status as possible reasons for graft failure or graft rejection after allo-HSCT in patients with TDT.[67,69–71,79,87,90,104,107,126]

In this SLR, variability in VOC occurrence and RBCT requirements following allo-HSCT could not be assessed by age groups, donor type, conditioning regimen, or variable follow-up period as the studies included mixed populations and did not consistently report results by these subgroups. However, it is important to reiterate that post- allo-HSCT VOCs in patients with SCD and RBCTs in patients with TDT maybe related to patient- and/or allo-HSCT- related factors.

Despite advances in prophylaxis and management, GVHD remains a critical complication after allo-HSCT with potential for significant morbidity and mortality. Additionally, GVHD treatment such as corticosteroids could result in adverse events such as infections due to prolonged use of immunosuppression.[148] Acute GVHD that affects up to 70% patients also results in poor prognosis after allo-HSCT.[149] Severe acute GVHD (Grade III–IV) is reported in up to 14% patients despite standard GVHD prophylaxis. These patients require aggressive immunosuppressive treatment, which increases the risk of infections and end organ damage and puts these patients at higher risk for developing chronic GVHD.[149] Chronic GVHD, a late complication of allo-HSCT, affects an estimated 30.0%–50.0% of allo-HSCT recipients and has the potential to substantially impact quality of life in affected patients.[150–154] Studies have observed chronic GVHD to be a leading cause of mortality among long-term (≥2 years) survivors of allo-HSCT.[155,156]

Results from this review also highlight the challenge associated with assessing the exact incidence of VOCs following allo-HSCT due to the lack of standardized outcome definitions and consistent outcome reporting. A prior SLR by Zaidi et al, conducted to assess frequency of VOCs in patients with SCD treated with standard of care in real-world settings, reported similar variability in VOC definitions.[20] Specifically, that review reported differences in VOC definitions across studies in terms of events that were classified as VOC and follow-up time for reporting VOCs. This current review also observed differences in VOC reporting among studies of patients with SCD after allo-HSCT. This review also observed potential for variable effectiveness findings of allo-HSCT in TDT due to differences in definition of transfusion independence/dependence, lack of consistent reporting of time from allo-HSCT to beginning of RBCT-free period, as well as duration of RBCT-free period that would deem patients to be transfusion independent. It is critical to develop and implement standardized definitions for outcomes to avoid reporting inconsistent or heterogeneous treatment effects of allo-HSCT.

There are some limitations to the current review. There was considerable heterogeneity in inclusion criteria for studies, age groups, conditioning regimens, donor sources, and follow-up period. Variability in outcome definitions for VOCs in SCD studies and RBCT requirements in TDT studies could impact comparisons of outcome results between studies; a meta-analysis was not conducted due to the likely lack of feasibility due to this clinical and methodological heterogeneity, and due to limitation from pooling of unadjusted results. Graft failure and graft rejection were summarized as reported in included studies. There is potential for misclassification of events between these categories if studies reported without differentiation of failure and rejection. Transplant outcomes were summarized only from publications that reported VOCs and RBCTs for SCD and TDT, respectively. There is potential for underestimation of transplant outcomes based on the study inclusion criteria for this review. Lack of standardized diagnostic practices and representation of geographies with highest burden of SCD and TDT such as sub-Saharan Africa or South Asia could potentially result in evidence gaps on the effectiveness of allo-HSCT and impact generalizability of results to these areas. Finally, only English language studies were included, so there is potential for publication bias even though studies were included from all countries.

In conclusion, synthesis of available evidence on disease-related outcomes shows that on average 1 in 14 patients with SCD continue to experience VOCs or acute pain episodes despite having stable donor-derived hematopoiesis, and on average 1 in 11 patients with TDT, mostly those with graft failure or rejection, continue to require RBCTs after allo-HSCT. This highlights that allo-HSCT may not be consistently successful in all transplanted patients, with the potential for residual disease burden in addition to significant transplant-related burden from graft failure/rejection, acute/chronic GVHD, infections, life-threatening organ damage, and mortality.

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