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The effectiveness of hematopoietic stem cell transplantation in treating pediatric sickle cell disease: Systematic review and meta-analysis

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ABSTRACT

Background: Patients with sickle cell disease (SCD) have just one recognized curative therapy option: hematopoietic stem cell transplantation (HSCT), which results in a long-lasting improvement in the clinical phenotype. Here, we assessed the effectiveness of HSCT in treating children with SCD by a systematic review and meta-analysis.

Methods: Up until January 2024, a comprehensive search was done using Web of Science, CINAHL, Embase, Google Scholar, Cochrane Library, PubMed/Medline, and Embase. Two reviewers worked separately to extract the data, and Newcastle-Ottawa Quality Assessment tool was used to assess the research's quality. The outcomes analyzed were Overall survival (OS), event-free survival (EFS), graft failure (GF) and mortality.

Results: Nineteen papers satisfied our inclusion requirements and were assessed to be of fair quality. The pooled rate of OS was high (92%; 95% CI: 90.3%–93.5%). Similar finding was detected for EFS (85.8%; 95% CI: 83.7%–87.7%). In the other hand, pooled rates of GF and mortality were 6.9% (95% CI: 5.3%–8.9%) and 7.4% (95% CI: 5%–10.7%), respectively. A significant publication bias was detected for OS, EFS and GF outcomes. Subgroups analysis showed that study design was the major source of heterogeneity.

Conclusion: Our results show that HSCT is effective and safe, with pooled survival rates above 90%. It is important to assess innovative tactics in light of the alarming GF and mortality rates.

1. Introduction

Sickle cell disease (SCD) is the most common hereditary hemoglobinopathy, affecting around 300,000 people globally. The condition is especially common in low-income nations (Wastnedge et al., 2018; Yawn et al., 2014). Numerous consequences, including organ damage, life-threatening illness, and shortened lifespan, are associated with this disease. Prophylactic use of penicillin, use of hydroxyurea, chronic blood transfusions, vaccinations, enhanced health maintenance surveillance programs, and approval of novel agents such as voxelotor, crizanlizumab, and L-glutamine are among the advancements in SCD prevention (Ataga et al., 2017; Niihara et al., 2018; Scothorn et al., 2002; Vichinsky et al., 2019; Ware and Helms, 2012). These developments have led to a change in the causes of SCD-related mortality, which are now systemic vasculopathies linked to cardiac, pulmonary, and renal involvement (Blinder et al., 2013; Payne et al., 2017). Despite this, SCD patients still have significant morbidity and short life expectancies.

Recently, the US Food and Drug Administration (FDA) has approved two landmark cell-based gene therapies, Vertex's Casgevy and bluebird bio's Lyfgenia, for treatment of SCD (Parums, 2024).

However, the current scientifically proven treatment for SCD that resolves the clinical phenotype is hematopoietic stem cell transplantation (HSCT). A patient with SCD and acute myeloid leukemia underwent the first successful HSCT in the United States in 1984 (De Montalembert et al., 1997). The majority of published evidence on HSCT's role in SCD occurs in the juvenile population, where myeloablative conditioning (MAC) regimens are frequently used. HSCT is

Abbreviations: ATG, anti-thymocyte globulin; BM, Bone marrow; CB, cord blood; EFS, event-free survival; GF, graft failure; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; MAC, myeloablative conditioning; MMUD, HLA-mismatched unrelated donor; MRD, HLA-matched related donor; MUD, matched unrelated donors; NMA, non-myeloablative; NOS, Newcastle-Ottawa Quality Assessment Scale; OS, Overall survival; PB, peripheral blood; RIC, reduced intensity conditioning; SCD, Sickle cell disease; UCB, Unrelated cord blood.

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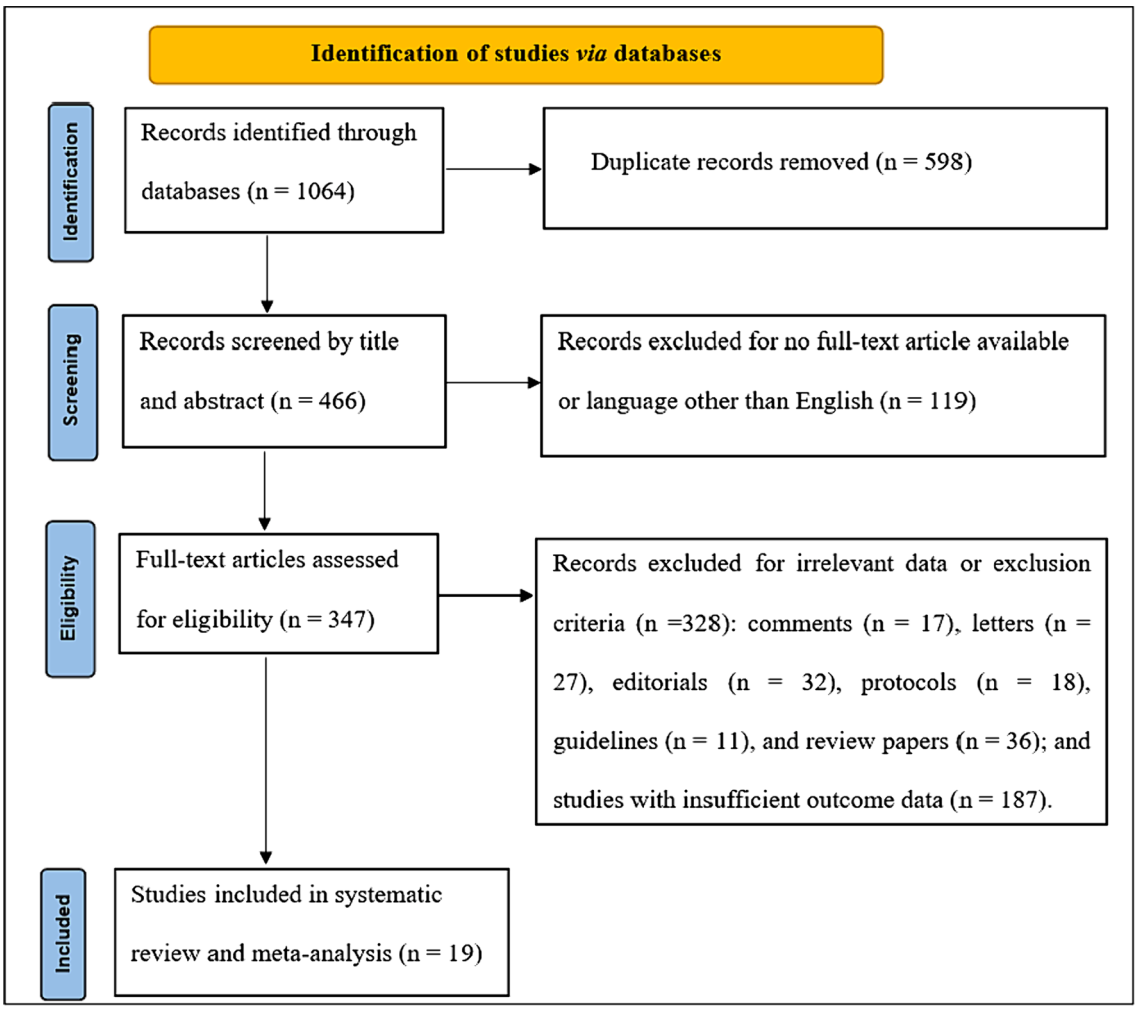

Fig. 1. PRISMA flowchart of this meta-analysis.

accompanied with considerable toxicities and even fatal complications, despite the fact that treatment is curative for the majority of patients. Consequently, the most commonly defined indications for HSCT include acute chest syndrome (ACS), cerebrovascular illness, priapism, severe alloimmunization, avascular necrosis, retinopathy, and diseases of the kidney and lungs (Flor-Park et al., 2022).

Research has demonstrated that HSCT carried out before the age of ten is linked to a lower risk of death and a lower overall health care expenditure (Arnold et al., 2017; Brazauskas et al., 2020).

Several studies have shown that HSCT, when performed on children with sickle cell disease (SCD), has favorable long-term outcomes, with over 90 % of transplants successful when a sibling who shares the same HLA is the donor (Dedeken et al., 2014; García Morin et al., 2017; Gouveia et al., 2023). However, there are still a number of barriers that prevent widespread use of HCT for the treatment of sickle cell disease (SCD). These comprise, among other things, the possibility of graft failure (GF), graft-versus-host disease (GVHD), and a lack of compatible related donors who match the patient's HLA, though the latter has recently improved due to the availability of haploidentical and matched unrelated donors (MUDs) (Bolaños-Meade et al., 2012; Dallas et al., 2013; Gluckman et al., 2017). Regrettably, individuals in low-income nations also have restricted access to HSCT, which raises the mortality rate from SCD (John et al., 2022; Krishnamurti, 2021).

At the moment, the suggested inclusion criterion for transplantation in SCD is <16 years of age (Bolaños-Meade and Brodsky, 2009). The best results are probably likely to occur at a young age at transplant before the beginning of serious chronic organ deterioration. As a result, it is critical to recognize SCD patients as potential candidates for HSCT as soon as possible (Walters et al., 1995). However, data about the totality of evidence pertaining to the efficacy of HSCT on children with SCD are limited. Therefore, this systematic review and meta-analysis study sought to assess the effects of HSCT on children with sickle cell disease in terms of overall survival, event free survival, graft failure and mortality.

2. Methods

This systematic review and meta-analysis study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards (Liberati et al., 2009).

2.1. Search strategy

From the time the database was built until January 2024, searches were conducted through CINAHL, PubMed/Medline, the Cochrane Library, Web of Science, Google Scholar, and Embase. The search strategy was created using the following terms: "hematopoietic cell transplantation" OR "HCT" OR "haematopoietic stem cell transplantation" OR "HSCT" AND "sickle cell disease" OR "SCD" AND "pediatric" OR "children". We also manually searched the references mentioned in narrative reviews and pertinent non-systematic papers to find further relevant studies that our search approach could have overlooked. The two authors carried out each retrieval method independently.

Table 1
Characteristics of included studies.

Study ID	Study design	Country	Sample size (sex)	Age, median (range), years	Stem cell source (n)	Donor status (n)	Conditioning intensity (n)	Median follow-up period (range), years	Outcomes (yr)
(Walters et al., 2001)	Prospective	USA	59 (M:36; F:23)	10.1 (3.3–15.9)	-BM (59)	-MRD (59)	-MAC (56) -RIC (3)	3.50 (0.9–9.5)	-OS -DFS -GF -Mortality (3.5 yr)
(Majumdar et al., 2010)	Retrospective	USA	10 (M:6; F:4)	10.1 (2.8–16.3)	-BM (6) -PB (2) -CB (1) -CB + BM (1)	-MRD (10)	-MAC (10)	5.5 (2.9–11)	-OS -DFS -GF -Mortality (5.5 yr)
(McPherson et al., 2011)	Retrospective	USA	27 (M:15; F:12)	9.7 (3.3–17.4)	-BM (27)	-MRD (27)	-MAC (27)	4.9 (1.0–10.0)	-OS -DFS -GF (5 yr)
Strocchio et al. 2015 (McPherson et al., 2011)	Retrospective	Italy	15 (M:10; F:5)	9.2 (1.7–16.5)	-BM (13) -BM + CB (1) -PB (1)	-MRD (9) -MUD (6)	-MAC (15)	10 (3–14)	-OS -DFS -GF (7 yr)
(Dallas et al., 2013)	Clinical trial	USA	22 (M:15; F:7)	10 (4.2–17.4)	-CB (1) -BM (13) - Haploidentical (8)	-Haploidentical (8) -MRD (14)	-MAC (14) -RIC (8)	9.0 ± 2.3	-OS -DFS -GF -Mortality (8 yr)
(Bhatia et al., 2014)	Prospective	USA	15 (M:13; F:2)	7.3 (2.3–16.3)	-BM (12) -CB (3)	-MRD (15)	-MAC (15)	2.9 (0.3–7.4)	-OS -DFS -GF (2 yr)
(Dedeken et al., 2014)	Retrospective	Belgium	50 (M:27; F:23)	8.3 (1.7–15.3)	-CB (3) -BM (39) -BM + CB (7) -PB (1)	-MRD (49) -Mismatched (1)	MAC (50)	7,7	-OS -DFS -GF -Mortality (8 yr)
(Lucarelli et al., 2014)	Prospective	Italy	40 (M:22; F:18)	12 (2–16)	-BM (40)	-MRD (40)	-MAC (40)	ND	-OS -DFS -GF -Mortality (5 yr)
(Maheshwari et al., 2014)	Retrospective	USA	15 (ND)	6 (1.2–15.5)	-BM (15)	-MRD (15)	-MAC (15)	3 (1.3–9)	-OS -DFS -GF (3 yr)
(Isgro et al., 2015)	Retrospective	Nigeria	31 (M:17; F:14)	10 (2–17)	-BM (31)	-MRD (31)	-MAC (31)	ND	-OS -DFS -GF -Mortality (4 yr)
(García-Morin et al. 2017)	Retrospective	Spain	11 (M:8; F:3)	7 (2–13)	-BM (11)	-MRD (11)	-MAC (11)	3.1 (1–5.7)	-OS -DFS -GF -Mortality (3 yr)
(Gluckman et al., 2017)	Retrospective	France	846 (M:416; F:430)	8.3 (0.3–16)	-BM (728) -PB (30) -CB (88)	-MRD (846)	-MAC (760) -RIC (85)	4.5 (0.25–27)	-OS -DFS (5 yr)
(Marzollo et al., 2017)	Retrospective	Italy	11 (M:4; F:7))	6.5 (3.9–16.3	-BM (6) -BM + CB (2) -PB (3)	-MRD (7) - Haploidentical (2) -MUD (1) -MMUD (1)	-RIC (11)	2.35 (0.8–6.5)	-OS -DFS -GF (2.4 yr)
(Alonso et al., 2019)	Retrospective	Spain	22 (ND)	8.6 (2.09–15)	-BM (19) -CB (2) -BM + CB (1)	-MRD (21) -CB (1)	-MAC (20) -Unknown (2)	ND	-OS -EFS -GF (3 yr)
(Eapen et al., 2019)	Retrospective	USA	673 (M:489; F:421)	ND	ND	ND	ND	ND	-OS -DFS -GF (3 yr)
(Guilcher et al., 2019)	Retrospective	Canada	15 (M:5; F:10)	12 (3–17)	-PB (15)	-MRD (15)	-NMA (15)	1.6 (1.2—2.3)	-OS -DFS -GF (1.6 yr)

(*continued on next page*)

Table 1 (*continued*)

Study ID	Study design	Country	Sample size (sex)	Age, median (range), years	Stem cell source (n)	Donor status (n)	Conditioning intensity (n)	Median follow-up period (range), years	Outcomes (yr)
(Benítez-Carabante et al., 2021)	Retrospective	Spain	45 (M:25, F:20)	9.13 (2.01—19.08)	-BM (42) -CB (2) -BM + CB (1)	-MRD (45)	-BuCy200 (27) -BuCy120 (4) -TreoFluThi (14)	3.4 (0.8 – 20.5)	-OS -EFS -GF -Mortality (3 yr)
(Parikh et al., 2021)	Clinical trial	USA	13 (M:4; F:9)	13 (3–17)	-UCB (13)	-Mismatched (13)	-MAC (13)	4 (2.3–7.5)	-OS -DFS -GF -Mortality (4 yr)
(Al-Jefri et al., 2022)	Retrospective	Saudi Arabia	25 (M:5, F:20)	10.6 (3.0–13.9)	-BM (25)	-MRD (25)	-MAC (19) -MAC without ATG (6)	4.35 ± 0.48	-OS -EFS -GF -Mortality (3 yr)

n: Number; M: Male; F: Female; MRD: HLA-matched related donor; BM: Bone marrow; MAC, myeloablative conditioning; ATG: anti-thymocyte globulin; CB: cord blood; ND: not defined; yr: years; RIC: reduced intensity conditioning; PB: peripheral blood; NMA: non-myeloablative; MUD: HLA-matched un-related donor; MMUD: HLA-mismatched unrelated donor; UCB: Unrelated cord blood.

2.2. Inclusion and exclusion criteria

Once duplicates were eliminated, relevant articles were filtered based on their title and abstract. Included studies were to discuss the results of HSCT in treating SCD in children. Next, to verify eligibility, the full texts of the remaining studies were reviewed.

Inclusion criteria for articles were: (1) observational studies (retrospective or prospective) reporting the outcomes of HSCT in pediatric SCD population (a cutoff of <18 years was used to define the pediatric age group); (2) studies with sample size ≥10; (3) publications reporting overall survival, event free survival, graft failure or mortality rate outcomes; (4) a median follow-up of at least 1 year; and (5) studies published as original articles. The exclusion criteria were as follows: (1) no full text available electronically; (2) publication in a language other than English; (3) comments, letters, editorials, protocols, guidelines, and review papers; and (4) studies with insufficient outcome data.

2.3. Data extraction

Following the inclusion and exclusion criteria, the two independent authors extracted data from the eligible papers. Following a standard data sheet, the information was collected and included the following: (1) Study ID (name of first author, year of publication), (2) study design, (3) country, (4) sample size (sex), (5) Age, median (range), years, (6) stem cell source (n), (7) donor status (n), (8) conditioning intensity (n), (9) median follow-up period (range), years, (10) outcomes.

2.4. Quality assessment of the studies

To evaluate the quality of the included publications, the Newcastle-Ottawa Quality Assessment Scale (NOS), intended for cohort studies, was employed. This assessment was done independently by the two authors, with disagreements resolved by discussion with a third volunteer author. Cohort selection, cohort comparability, and outcome evaluation are the three evaluation components of the NOS. A quality result can be rated as poor (maximum score in one or none of the categories), fair (maximum score in two areas, one of which had to be the comparability section), or good (maximum score in all sections) (Stang, 2010).

2.5. Statistical analysis

Comprehensive Meta-Analysis version 3 (Biostat Inc. USA) was used for the statistical analysis. Proportions for each specific outcome of interest were calculated. By using the Freeman-Tukey variant of the arcsine square root-transformed proportion, quantities were derived from proportions (Lin and Xu, 2020). The weighted mean of the altered proportions was back-translated using DerSimonian and Laird's random-effects model to determine the pooled proportion. $P < 0.05$ was established as the threshold for significance. The Cochrane chi-squared test was used to measure the heterogeneity across the studies; a P-value < 0.05 indicated the presence of heterogeneity. To evaluate the impact of heterogeneity on the meta-analysis, the I^2 value was calculated. I^2 values > 50 % and $P < 0.05$ showed that there was moderate to high degrees of heterogeneity among pooled studies. A fixed-effects design was used when $I^2 < 50$ % and $P > 0.05$; in other cases, a random-effects model was applied (Borenstein et al., 2010). We also performed subgroup analysis to assess the possible sources of heterogeneity. Using Egger's test, publication bias was evaluated. A visual analysis of funnel plot symmetry was also employed to assess publication bias in more detail.

3. Results

Out of the 1064 studies we selected for screening, a total of 347 abstracts were determined to be potentially eligible and retrieved for full text examination. This systematic review and meta-analysis study comprised a total of nineteen papers that satisfied the inclusion criteria. The PRISMA flowchart is shown in Fig. 1.

3.1. Characteristics of included studies

The included papers were distributed among 8 countries: USA (n = 8), Italy (n = 3), Spain (n = 3), Canada (n = 1), Belgium (n = 1), France (n = 1), Nigeria (n = 1), Saudi Arabia (n = 1) and published between 2001 and 2022 and. Among 19 articles, 14 were retrospective, 3 were prospective and 2 were clinical trials. The sample sizes of the included studies ranged from 10 to 846 patients, with a total of 1945 individuals. The participants' median age ranged from 6 (1.2–15.5) to 13 (3–17). Generally, bone marrow was the source of stem cells. A myeloablative regimen was used to condition the majority of patients, and the majority of donors were related donors with HLA matching. The interval of follow-up ranged from 1.6 to 10 years.

Characteristics of included studies are summarized in Table 1.

3.2. Quality assessment

All studies were assessed to be of fair quality because they scored maximum score in two sections: comparability and outcomes sections (Table 2).

Table 2
Newcastle-Ottawa quality assessment scale for cohort studies included in the meta-analysis.

Study	Selection				Comparability	Outcome			Quality score
	Representativeness of the sample	Selection of the non-exposed group	Ascertainment of exposure	Outcome not present at the start of study		Evaluation of the outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up	
(Al-Jefri et al., 2022)	★	0	★	★	★★	★	★	★	Fair
(Alonso et al., 2019)	★	0	★	★	★★	★	★	★	Fair
(Benítez-Carabante et al., 2021)	★	0	★	★	★★	★	★	★	Fair
(Bhatia et al., 2014)	★	0	★	★	★★	★	★	★	Fair
(Dallas et al., 2013)	★	0	★	★	★★	★	★	★	Fair
(Dedeken et al., 2014)	★	0	★	★	★★	★	★	★	Fair
Eapen et al., 2019 (Eapen et al., 2019)	★	0	★	★	★★	★	★	★	Fair
García-Morin et al. 2017	★	0	★	★	★★	★	★	★	Fair
(Gluckman et al., 2017)	★	0	★	★	★★	★	★	★	Fair
(Guilcher et al., 2019)	★	0	★	★	★★	★	★	★	Fair
(Isgro et al., 2015)	★	0	★	★	★★	★	★	★	Fair
(Lucarelli et al., 2014)	★	0	★	★	★★	★	★	★	Fair
(Maheshwari et al., 2014)	★	0	★	★	★★	★	★	★	Fair
(Majumdar et al., 2010)	★	0	★	★	★★	★	★	★	Fair
(Marzollo et al., 2017)	★	0	★	★	★★	★	★	★	Fair
(McPherson et al., 2011)	★	0	★	★	★★	★	★	★	Fair
(Parikh et al., 2021)	★	0	★	★	★★	★	★	★	Fair
Strocchio et al. 2015 (McPherson et al., 2011)	★	0	★	★	★★	★	★	★	Fair
(Walters et al., 2001)	★	0	★	★	★★	★	★	★	Fair

3.2.1. Selection

Three stars were awarded to each study. Every study had its exposure assessed using secure records, and precautions were made to ensure that results of interest were not present at the beginning of the research. The lack of a non-exposed group (control group) was the reason the selection part did not receive a full quality score.

3.2.2. Comparability

Each study received a two-star rating after controlling for the outcomes and other variables like age.

3.2.3. Outcome

For using a validated assessment tool, demonstrating a follow-up period long enough for outcomes to occur (>1 year), and demonstrating a complete follow-up period, all the studies received three stars.

3.3. Outcomes

3.3.1. Overall survival

The OS rate was reported in nineteen studies (Fig. 2). Given the significant heterogeneity indicated by the Cochran's Q test and I^2 statistic (Q = 86.13, p = 0.000, I^2 = 79 %), a random model was chosen. According to the forest plot analysis, the pooled OS rate was 92 % (95 % CI: 90.3 %–93.5 %). The statistically significant findings of the Egger's test demonstrated publication bias (p = 0.000). The asymmetric funnel plot provided evidence for this finding (Fig. 3).

3.3.2. Event free survival

The EFS rate was reported in nineteen studies (Fig. 4). Given the significant heterogeneity indicated by the Cochran's Q test and I^2 statistic (Q = 110.67, p = 0.000, I^2 = 83 %), a random model was selected. According to the forest plot analysis, the pooled EFS rate was 85.8 % (95

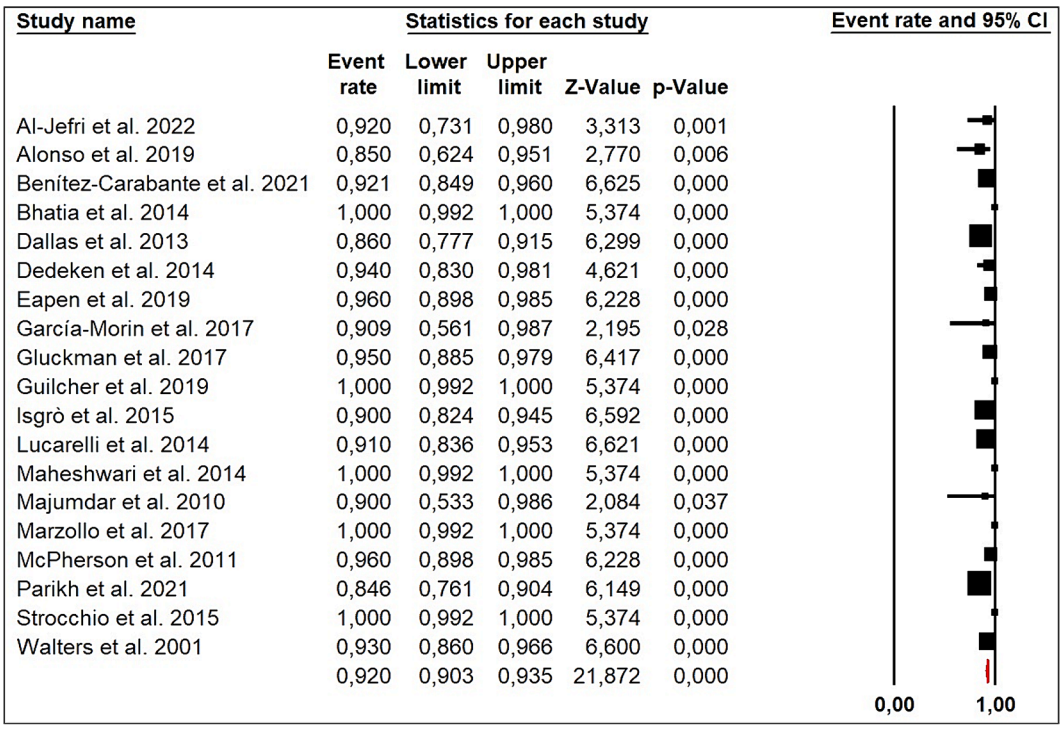

Fig. 2. Forest plot of pooled OS rate.

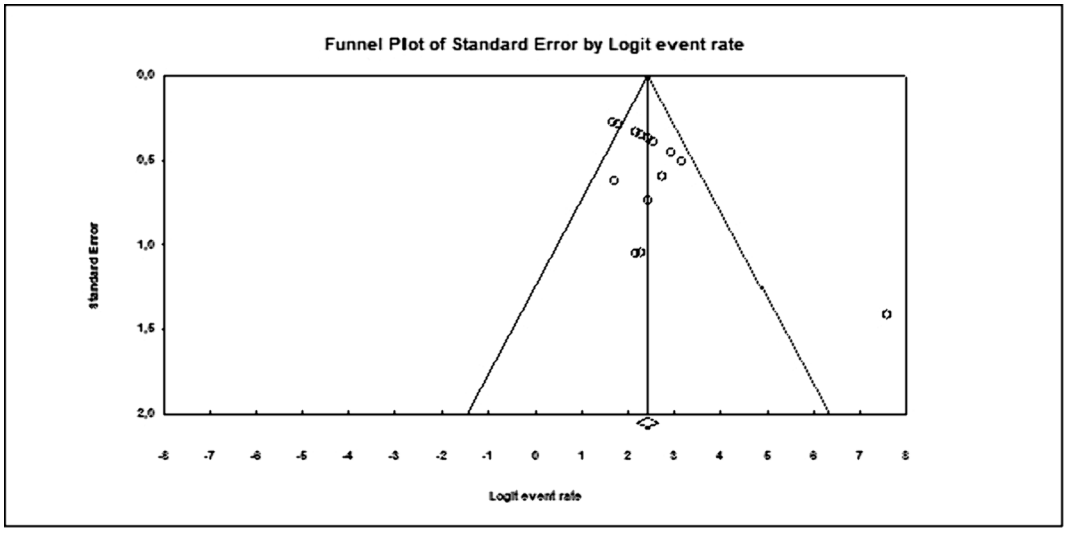

Fig. 3. OS rate pooled in a funnel diagram. The nineteen included studies are shown as circles. The horizontal axis shows the OS rate while the vertical axis indicates the standard error. The effects summary estimate is represented by the vertical line, while the 95% CI of the standard error are represented by the two lines on either side.

% CI: 83.7 %–87.7 %). The statistically significant findings of the Egger's test demonstrated publication bias (p = 0.000). This conclusion was corroborated by the asymmetrical funnel plot (Fig. 5).

3.3.3. *Graft failure*

The GF rate was reported in eighteen studies (Fig. 6). Because of the significant heterogeneity indicated by the Cochran's Q test and I^2 statistic (Q = 100.05, p = 0.000, and I^2 = 83 %), a random model was used. According to the forest plot analysis, the pooled GF rate was 6.9 % (95 % CI: 5.3 %–8.9 %). The statistically significant findings of the Egger's test demonstrated publication bias (p = 0.000). The asymmetric funnel plot provided evidence for this finding (Fig. 7).

3.3.4. *Mortality*

The mortality rate was recorded in ten studies (Fig. 8). Because of the significant heterogeneity indicated by the Cochran's Q test and I^2 statistic (Q = 100.05, p = 0.000, and I^2 = 83 %), a random model was used. According to the forest plot analysis, the pooled death rate was 7.4 % (95 % CI: 5 %–10.7 %). The lack of statistical significance in the Egger's test results indicated that there was no indication of publication bias (p = 0.412). The symmetry of the funnel plot confirmed this finding (Fig. 9).

3.4. *Subgroup analysis*

There was little difference in the occurrence rates of OS, GF, and

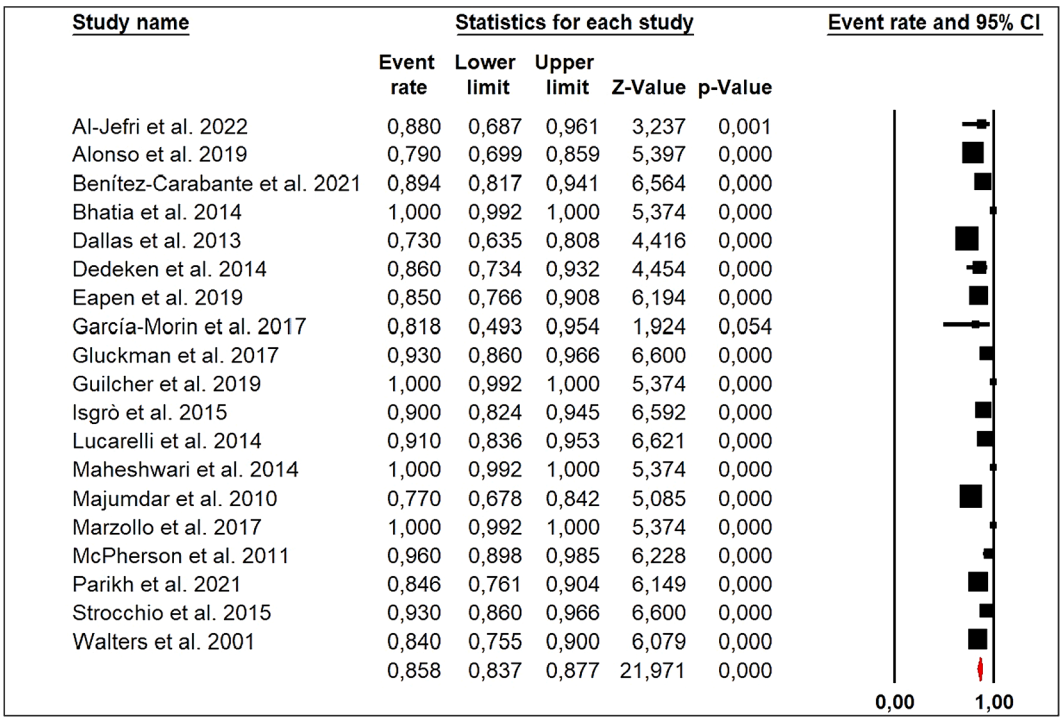

Fig. 4. Forest plot of pooled EFS rate.

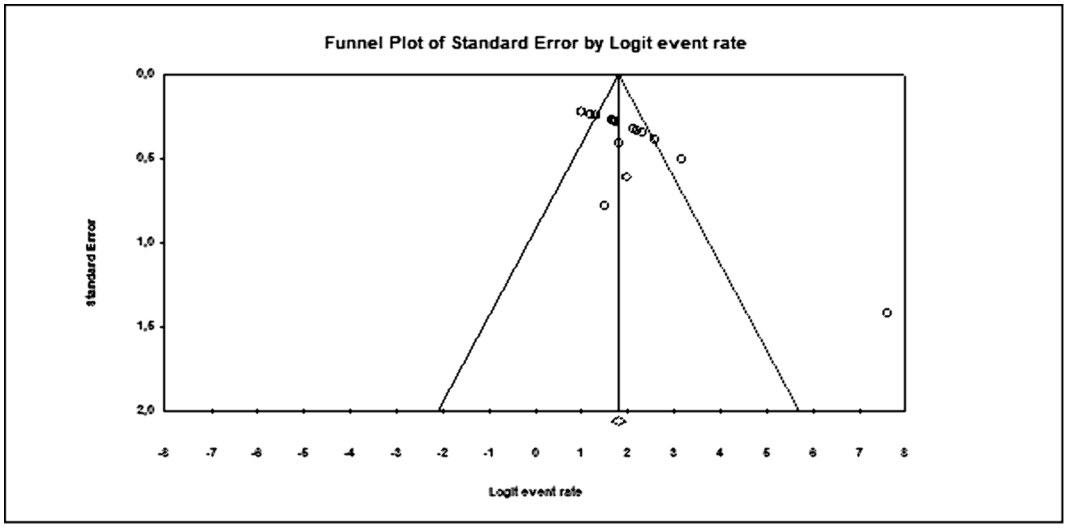

Fig. 5. EFS rate pooled in a funnel diagram. The nineteen included studies are shown as circles. The horizontal axis shows the EFS rate while the vertical axis indicates the standard error. The effects summary estimate is represented by the vertical line, while the 95% CI of the standard error are represented by the two lines on either side.

mortality comparing studies published prior to and following 2015 ($p > 0.05$). However, compared to studies published prior to 2015, the occurrence rate of EFS was much higher in those published after 2015 (87.7% versus 83,4%, $p = 0.035$). The event rates of OS, EFS, and GF were significantly different between retrospective, prospective, and clinical trial studies ($p < 0.05$). But there was no discernible variation in the mortality rate ($p > 0.05$). Furthermore, no significant difference was detected in the event rates of OS, EFS and mortality outcomes according to geographical origin of publications ($p > 0.05$). However, the highest GF event rate was observed in American countries (86 %), followed by European countries (50 %) (Table 3).

4. Discussion

Globally, sickle cell disease is the most prevalent hemoglobinopathy (Piel et al., 2013). Many nations have instituted newborn screening programs, which have resulted in early disease detection and early interventions (García-Morín et al., 2020). Reduced life expectancy, quality-adjusted life expectancy, and lifetime earnings were some of the effects of SCD on society (Lubeck et al., 2019). These findings suggest that improving SCD morbidity and mortality will require disease-modifying treatments (Bernaudin et al., 2019).

Hematopoietic stem cell transplantation is the sole treatment available to SCD patients; yet, its use is restricted due to the lack of knowledge about its possible advantages and the shortage of donors with the

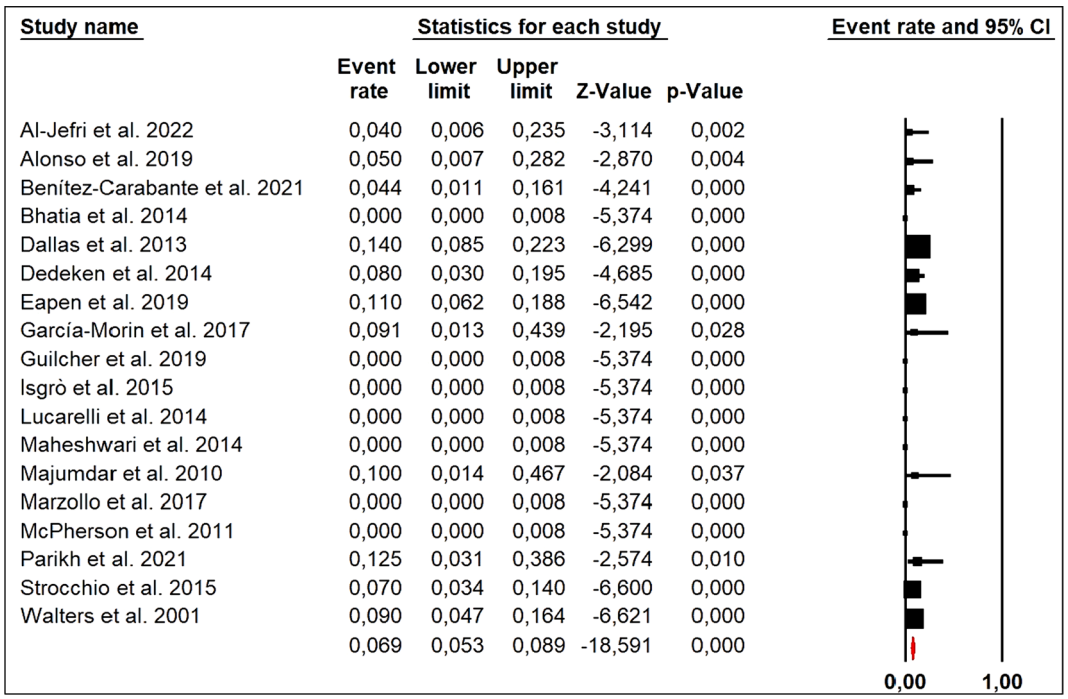

Fig. 6. Forest plot of pooled GF rate.

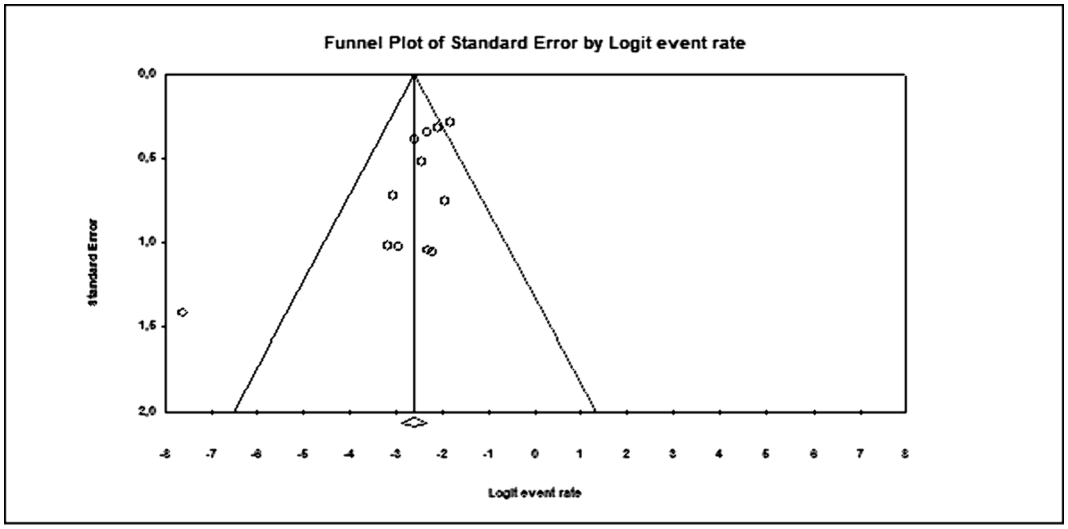

Fig. 7. GF rate pooled in a funnel diagram. The eighteen included studies are shown as circles. The horizontal axis shows the GF rate while the vertical axis indicates the standard error. The effects summary estimate is represented by the vertical line, while the 95% CI of the standard error are represented by the two lines on either side.

same HLA (Alonso et al., 2019). A few studies, including this one, looked at the outcomes of HSCT in young SCD patients (Iqbal et al., 2021). Our findings suggest that for children with severe SCD, HSCT provides a treatment alternative and a risk–benefit balance (Bernaudin et al., 2019; Gluckman et al., 2017; Locatelli et al., 2013). Having a donor chimerism following HSCT enables the creation of normal hemoglobin chains and eliminates SCD patients' symptoms. Patients with sickle cell disease have been demonstrated to have a disease-free survival rate of more than 90 % when a transplant is performed on a young patient with minimum concurrent morbidity, the donor is an identical HLA sister, and the source is bone marrow. After transplantation, the risks of morbidity and death are higher among those with multiple morbidities or when various donors are used. Thanks to improved patient classification and better support care, HSCT outcomes have considerably improved over the past ten years. This meta-analysis study showed that there was a tendency toward improved outcomes in terms of both OS (92 %) and EFS (85.8 %). Our findings are similar to those reported in the literature (Vermylen et al., 1998; Walters et al., 2000). The potential reasons of this tendency were not examined in this work. The fact that so few haemoglobinopathy patients have an identical HLA family donor presents a challenge to their transplantation. Additionally, the patient's ethnicity has a significant impact on the likelihood of finding an unrelated donor. One possible benefit of using haploidentical donors or umbilical cord blood units is that more patients may be able to receive a transplant. These transplants haven't been used much because they've been linked to poor immunological reconstitution, GVHD, and an increased likelihood of implant failure. Over the past ten years, numerous authors who have documented positive outcomes in SCD

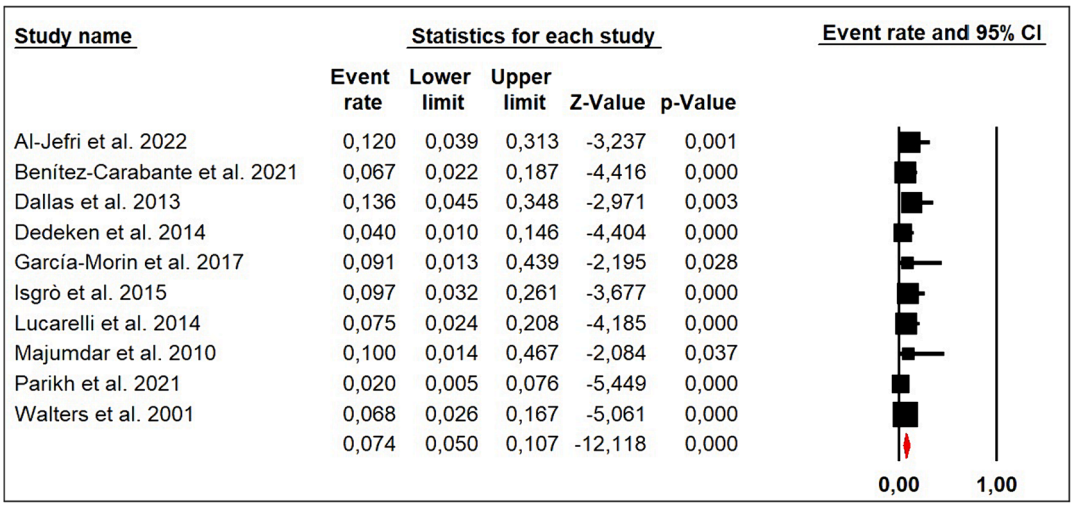

Fig. 8. Forest plot of pooled mortality rate.

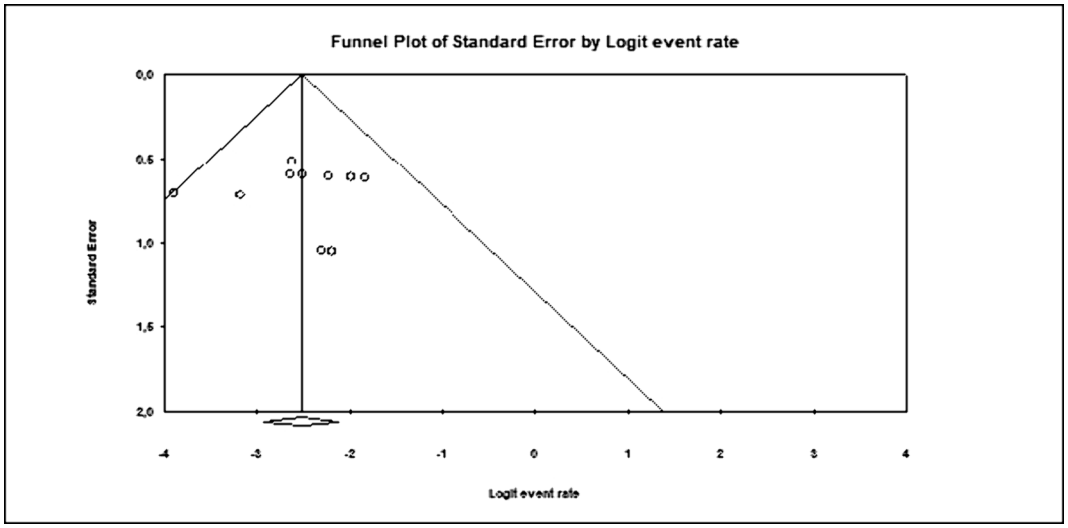

Fig. 9. Mortality rate pooled in a funnel diagram. The ten included studies are shown as circles. The horizontal axis shows the mortality rate while the vertical axis indicates the standard error. The effects summary estimate is represented by the vertical line, while the 95% CI of the standard error are represented by the two lines on either side.

patients have become interested in the developments in HLA typing, umbilical cord unit selection, GVHD prophylaxis and treatment, anti-HLA antibody research, and supportive and anti-infective therapies. Because of the risk involved, they are still regarded as experimental operations (Gluckman, 2013; Gluckman et al., 2017; Ruggeri et al., 2011). Here, we observed a low rate of GF (6.9 %) and mortality (7.4 %). Studies have shown that endothelial dysfunction and rejection, which increase the risk of death from transplantation, are more common in older individuals. Vermyeln et al. revealed that younger patients, who had the disease at an earlier stage, had the greatest outcomes (Vermylen et al., 1998). Regretfully, a patient with SCD has an 18 % chance of having a healthy MSD (Besse et al., 2016). As a result, during the past ten years, research has been done on many substitute platforms. It is uncommon to find a MUD donor (Krishnamurti et al., 2003), and poor engraftment has been linked to the use of unrelated matched donors. (Eapen et al., 2019). Recently, haploidentical transplantation has made HSCT more applicable to patients who do not have a matching HLA-matched donor. However, because GF is so common (40–50 %), it continues to be a serious concern in haploidentical donors (Bolaños-Meade et al., 2012). Notably, the GF rate and related CB have been abnormally high thus far (Ruggeri et al., 2011). Innovative approaches to lower the likelihood of graft rejection, like adding thiotepa or increasing the amount of total body irradiation, have shown encouraging results (Bolaños-Meade et al., 2019).

Most of the research that was covered under this meta-analysis made use of MAC HCT. According to newly published studies, adopting RIC/NMA regimens in pediatric and adult populations can reduce both short- and long-term organ toxicities (Bhatia et al., 2014). These studies demonstrated decreased mortality rates with comparable OS and DFS when compared to MAC regimens that used MRDs as the donor source. Higher GF rates were linked to earlier RIC regimes (Iannone et al., 2003). Another thing to think about is the timing of allo-HCT. Every ten years of age, the death rate in SCD patients rises significantly, most likely as a result of accumulated end-organ damage. Transplants done early in life are linked to better outcomes (Cappelli et al., 2019).

When compared to existing treatments, HSCT appears to be a promising alternative for children with severe sickle cell disease (SCD); nonetheless, its application is presently restricted to clinical protocols and reference facilities.

Table 3
Subgroup analysis.

Variable	Subgroups	Overall survival			Event free survival			Graft failure			Mortality rate		
		Number of studies	Event rate (95 % CI)	Difference between subgroups	Number of studies	Event rate (95 % CI)	Difference between subgroups	Number of studies	Event rate (95 % CI)	Difference between subgroups	Number of studies	Event rate (95 % CI)	Difference between subgroups
Year of publication	<2015	8	0.922 (0.895–0,943)	0.847	8	0.834 (0.799–0.864)	0.035	8	0.076 (0.053–0.107)	0.439	5	0.077 (0.045–0.128)	0.821
	⩾2015	11	0.919 (0.894–0.938)		11	0.877 (0.851–0.899)		10	0.062 (0.043–0.090)		5	0.070 (0.040–0.120)	
Study design	Retrospective	14	0.944 (0.925–0.958)	0.000	14	0.873 (0.849–0.894)	0.003	13	0.053 (0.037–0.075)	0.004	6	0.081 (0.047–0.134)	0.858
	Prospective	3	0.931 (0.891–0.957)		3	0.884 (0.835–0.921)		3	0.053 (0.028–0.096)		2	0.071 (0.034–0.141)	
	Clinical trial	2	0.853 (0.797–0.896)		2	0.782 (0.718–0.835)		2	0.138 (0.086–0.213)		2	0.061 (0.025–0.141)	
Continent	Europe	8	0.934 (0.906–0.953)	0.598	8	0.883 (0.853–0.908)	0.058	7	0.050 (0.030–0.080)	0.001	4	0.064 (0.034–0.118)	0.730
	America	9	0.914 (0.887–0.935)		9	0.832 (0.800–0.860)		9	0.086 (0.063–0.116)		4	0.067 (0.036–0.121)	
	Africa	1	0.900 (0.824–0.945)		1	0.900 (0.824–0.945)		1	0.000 (0.000–0.008)		1	0.097 (0.032–0.261)	
	Asia	1	0.920 (0.731–0.980)		1	0.880 (0.687–0.961)		1	0.040 (0.006–0.235)		1	0.120 (0.039–0.313)	

5. Strength and limitations

Six distinct databases were searched for relevant literature for this investigation. Consequently, 19 relevant papers were found to be eligible and met the inclusion criteria. This study does have certain drawbacks, though. Due to the large number of entries that were removed because they were not full-text available, some important study findings may have been overlooked. Publication bias most likely played a role in the non-significant outcomes being less representative because the data included in this meta-analysis were published. Measuring heterogeneity in meta-analysis is essential to evaluate the validity and reliability of results. It helps to determine whether the studies are sufficiently similar or comparable to be pooled together, and whether the meta-analysis results reflect a true effect or a random variation. It is extremely challenging to do a meta-analysis on HSCT among SCD patients due to in the heterogeneity of the demographic data, donor status, and source of stem cells. The utilization of multiple conditioning regimens constituted an additional disadvantage. The heterogeneity in this meta-analysis were largely caused by these differences, which also make pooled analysis more difficult and make it difficult to compare the findings of various research. The interpretation of the results may therefore be affected by the notable heterogeneity that characterizes meta-analysis research (Imrey, 2020). Consequently, the results of the current investigation need to be carefully considered. Thus, to better understand the effectiveness of HSCT among patients with SCD, future research should adhere to standardized methodology and reporting.

6. Conclusion

With a good prognosis, HSCT is a curative therapy for young SCD patients. SCD is increasingly being used as an indication of HSCT in several countries. The results of this study are in line with other studies and offer a basis for trying to improve these patients' outcomes. Because of the excellent EFS and OS, as well as the low risk of GF and mortality in younger patients, referrals to HSCT clinics should be recommended early in life, before significant problems arise. The purpose of innovative approaches to increase the number of patients who can receive HSCT must be investigated further.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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