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REVIEW OPEN ACCESS

Hematopoietic Stem Cell Transplantation Outcomes in Diamond–Blackfan Anemia Patients Based on Myeloablative Conditioning Regimen With or Without Total Body Irradiation: A Systematic Review and Meta-Analysis

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ABSTRACT

Diamond–Blackfan anemia (DBA) is a rare, congenital bone marrow failure syndrome characterized by hypoplastic anemia. Earliest descriptions of this disease date back to 1936, and since then, a plethora of treatment strategies have been used to control or treat the disease. In recent decades, hematopoietic stem cell transplantation (HSCT) has been declared the only curative treatment. Despite the time elapsing from the first time HSCT has been used in this setting, no unified standard preparative and prophylactic protocol has been established. In this article, for the first time, the published articles concerning the efficacy of the most verified conditioning regimens established for these patients, the myeloablative conditioning regimen (MAC), were systematically reviewed. A comparison of two groups, based on the presence or absence of radiation in their protocol, was performed. Electronic and manual searches were conducted on PubMed, Scopus, and Web of Science. The primary study domains, selection, and outcome were assessed using the JBI Scale quality assessment for cohort and case series studies. Cohorts were categorized into treatment groups, and the characteristics of patients and donors, in addition to intervention characteristics and outcomes, were synthesized. Among a total of 196 studies reviewed, we included five cohorts in our systematic review. The studies were heterogeneous in various aspects. In conclusion, our analysis suggests that DBA patients who underwent a MAC non-total body irradiation (TBI) conditioning regimen may experience better post-HSCT outcomes; however, the findings are inconclusive.

Abbreviations: aGvHD, acute graft-versus-host disease; ALG, anti-lymphocyte globulin; Ara-C, cytarabine; ATG, anti-thymocyte globulin; BM, bone marrow; BU, busulfan; cGvHD, chronic graft-versus-host disease; CsA, cyclosporine; CY, cyclophosphamide; DBA, Diamond–Blackfan anemia; ES, engraftment syndrome; FLU, fludarabine; HLA, human leukocyte antigens; HSCT, hematopoietic stem cell transplantation; MEL, melphalan; mPSL, methylprednisolone; MTX, methotrexate; OS, overall survival; PB, peripheral blood; PCI, pneumatosis cystoides intestinalis; PRES, posterior reversible encephalopathy; RRT, regimen-related toxicity; SAE, severe adverse event; SOS, sinusoidal obstructive syndrome; TAI, thoracoabdominal irradiation; TBI, total body irradiation; TREO, treosulfan; TT, thiotepa.

1 | Introduction

Diamond–Blackfan anemia (DBA) is a rare, inherited disorder characterized by bone marrow failure (BMF) syndrome. Even though in 1936 it was originally regarded as congenital hypoplastic anemia, in 2005 it was recategorized as the first human ribosomopathy disorder ever discovered [1–4]. DBA is an exceedingly rare illness, with an incidence rate of two to eight per million live births per year. DBA usually presents with severe anemia in early infancy.

To date, all reported mutations have been heterozygous in an autosomal recessive pattern. Heterozygous allelic variations in ribosomal protein (RP) genes are the most frequent genetic mutations in these patients. So far, more than 20 genes from this family have been discovered in relation to DBA, with majority of mutations affecting RPS19. In some cases, other gene mutations such as P53, GATA, and adenosine deaminase (ADA) mutations are the prerequisite for disease development. Defects in ribosomal proteins give rise to nuclear stress, which engenders cell-cycle arrest and apoptosis in hematopoietic stem and progenitor cells (HSPC) [1, 2, 4]. Hence, DBA patients are considered highly at risk for developing acute myeloid leukemia (AML) and osteogenic sarcoma in later life [1, 2].

The apt treatment of DBA requires a multi-faceted approach that covers an array of hematological and non-hematological concerns, such as diabetes, growth problems, and iron overload. Supportive care for these patients includes blood transfusion and steroid therapy. Patient's age is the main deciding factor in the recommended intervention method utilized. Regardless, hematopoietic stem cell transplantation (HSCT) is the only curative treatment in DBA patients [2, 3]. The first HSCT for DBA was performed in 1976, and HSCT has been proclaimed as the most efficacious treatment for DBA patients ever since. Earliest published data show 87% of overall survival (OS) after HSCT from human leukocyte antigens (HLA)-matched related donors (MRD) and 14% of OS after HSCT from alternative donors [4]. The outcomes of HSCT have improved in DBA patients in the past two decades, which has been ascribed to enhanced donor–recipient HLA matching, the development of high-resolution HLA typing, and more effective conditioning regimens and supportive care [3, 4].

While graft-versus-host disease (GvHD) is a primary clinical concern following allogeneic HSCT (allo-HSCT), regimen-related toxicities (RRT) and other associated adverse events warrant significant consideration. According to the current proposed guidelines regarding HSCT conditioning for DBA patients, the most common regimen is myeloablative conditioning regimen (MAC). This regimen consists of fludarabine (FLU)- and busulfan (BU)-based protocols as the backbones, with or without the addition of other chemotherapy agents. According to some studies, treosulfan might show less toxicity and is associated with better OS than BU. FLU is a purine analog, which is also well-tolerated with all alkylating agents to inhibit DNA repair, but not enough data have been published to systematically analyze the conditioning regimen efficacy in these patients [4, 5].

In this article, we systematically compared HSCT outcomes such as GvHD, OS, and other transplantation-related mortalities (TRM) in DBA patients in two groups: the MAC regimen with total body irradiation (TBI) and the MAC regimen without TBI [1, 3–5].

2 | Methods

2.1 | Protocol and Registration

This paper adhered to the latest Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14]. We registered the paper on PROSPERO with CRD42024529172 ID.

2.2 | Eligibility Criteria

Any study conducted between 1990 and 2024 that reported the outcomes of HSCT on DBA patients using MAC regimen with or without TBI was included, regardless of its prospective or retrospective design, as long as the data were classified and specific enough, and had a minimum of 10 patients.

PICO framework:

Participants: DBA patients

Intervention: HSCT with TBI

Comparison: HSCT without TBI

Outcome: acute and chronic graft-versus-host disease (aGvHD and cGvHD) after HSCT, engraftment status, GF, OS.

2.3 | Information Resources

An electronic search was conducted in PubMed, Scopus, and Web of Science from January 3, 2024 to January 6, 2024.

2.4 | Search Strategy

We searched all databases using the following three main terms: "hematopoietic stem cell transplantation", "Diamond–Blackfan anemia," and "conditioning regimen." Table S1 presents the systematic search string.

To maximize the sensitivity of the study selection, a manual search of citation lists and references within the included articles was conducted. Articles identified through this process were then assessed for eligibility based on the predefined inclusion criteria.

2.5 | Collection and Selection Process

Retrieved publications from all databases were imported into EndNote 21 Reference Management Software. Duplicate primary publications were subsequently removed. Study screenings were conducted independently by two reviewers based on the title and abstract. Eligible studies were subsequently selected for inclusion, with any discrepancies resolved through discussion and consensus. In cases where consensus could not be reached, a third expert reviewer was consulted. Data extraction was

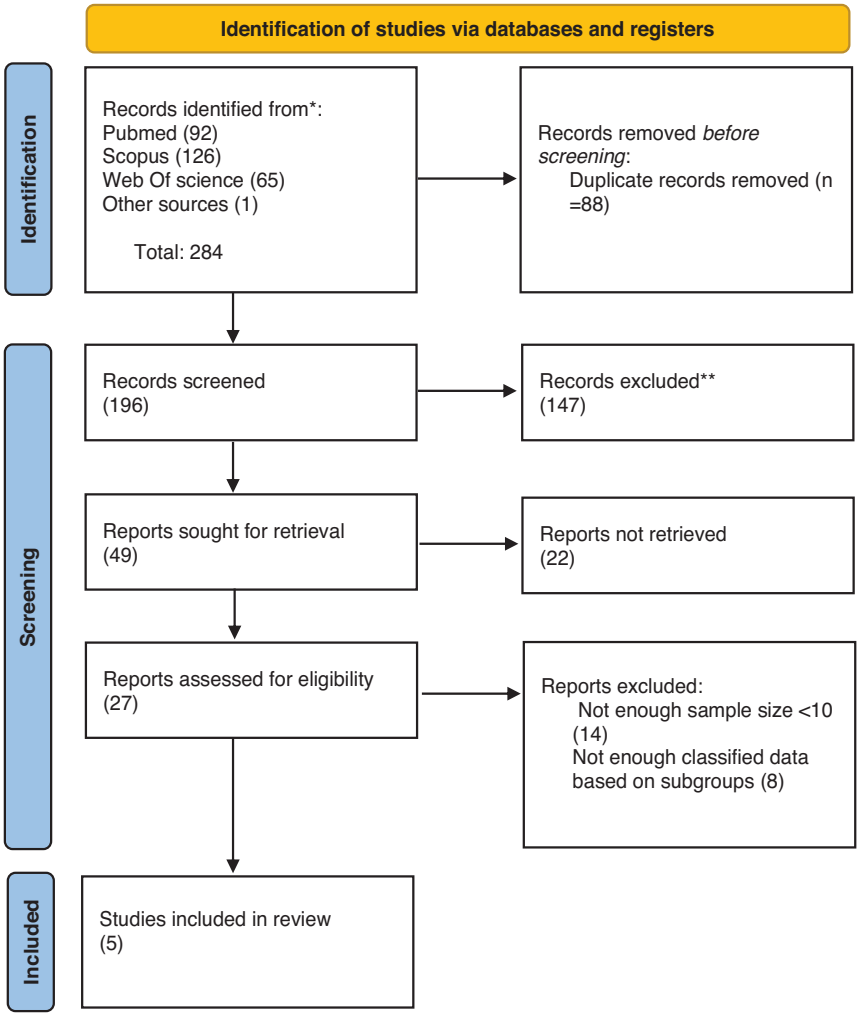

FIGURE 1 | Prisma flowchart.

performed independently by the two reviewers using a predefined extraction template implemented in Microsoft Excel. Extracted data items are summarized in Table S2. EndNote 21 was utilized for article archival and management. A PRISMA flow diagram documents the number of articles retrieved from each electronic database.

2.6 | Risk of Bias Assessment

Two reviewers independently assessed the risk of bias (ROB) using the official JBI Quality Assessment scale for cohort and case studies. In the case of any disagreements, a third expert reviewer was referred (https://jbi.global/critical-appraisal-tools).

2.7 | Data Synthesis

Data from each cohort study or non-randomized clinical trial were extracted and categorized. When applicable, the following variables were summarized for Diamond–Blackfan anemia (DBA) patients undergoing HSCT, stratified by conditioning regimen (with and without radiation): donor status, bone marrow source, prevalence of aGvHD, cGvHD, engraftment status, and graft failure (GF), as well as regimen-related toxicities, secondary malignancies, and mortality rates

3 | Results

3.1 | Study Selection and Characteristics

A comprehensive search in PubMed, Scopus, and Web of Science identified 92, 126, and 65 records ($n = 283$), respectively. Only one record was added manually, bringing the number of articles to 284.

Five cohort studies/non-randomized clinical trials were included in this study, as depicted in the PRISMA flow diagram (Figure 1). These studies included a cohort study or non-randomized clinical trial design and encompassed 84 patients who underwent HSCT following MAC regimens. The baseline and clinical characteristics of these five studies are summarized in Tables 1–4.

3.2 | Risk-of-Bias Assessment

Tables S3 and S4 provide the details on the JBI quality assessment of the included cohorts. Overall, the studies had low quality due

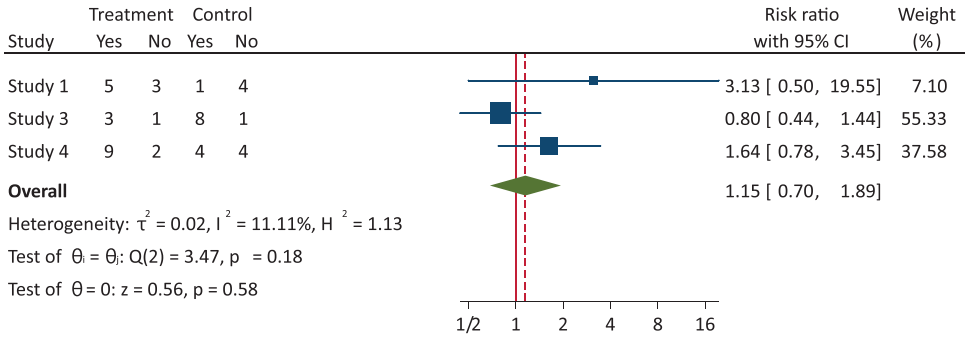

FIGURE 2 | Forest plot diagram for aGvHD/overall risk ratio = 1.15 [95% CI: 0.70, 1.89]. As the overall CI crosses 1, the result is not statistically significant. Although heterogeneity (I^2) is low (11.11%), the individual studies show a mix of effects. Overall, the pooled estimate does not suggest a significant association between treatment and control groups.

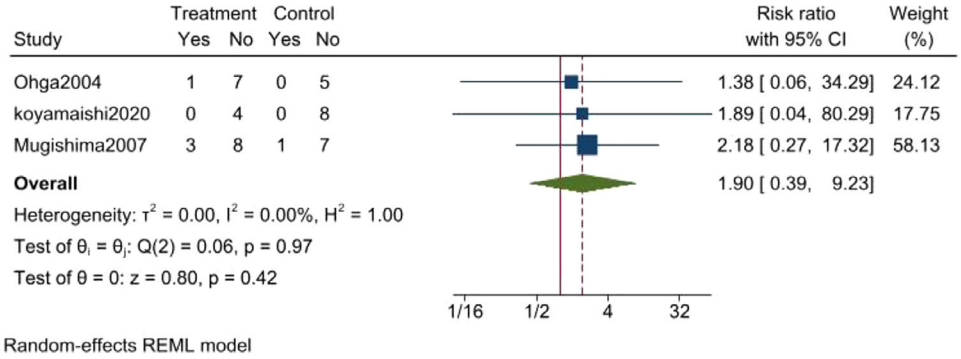

FIGURE 3 | Forest plot diagram for mortality/overall risk ratio = 1.90 [95% CI: 0.39, 9.23]. As the overall CI crosses 1, the result is not statistically significant. Heterogeneity (I^2) is close to 0. The individual studies show positive associations. Overall, the pooled estimate does not indicate a significant association between the intervention and mortality rate.

to allocation methods and statistical analysis, and the influence of confounders could not be overlooked (Figures 2 and 3).

3.3 | Study Results

Table 3 illustrates severe adverse events (SAEs), GvHD incidence, and mortality rates stratified by MAC regimen protocol (with and without TBI). While aGvHD demonstrated a slightly higher prevalence in the MAC-TBI group, cGvHD was more frequently observed in the MAC non-TBI group. Although the MAC-TBI group exhibited a higher mortality rate, this difference was not statistically significant. The incidence of both primary and secondary GF was greater in patients receiving the MAC-TBI protocol compared to those receiving the MAC non-TBI protocol.

3.4 | Studies Based on MAC-TBI and MAC Non-TBI Protocols

Three of five studies that were included encompassed both MAC-TBI and MAC non-TBI conditioning regimens [7, 15, 16], and patients in two other studies only received MAC non-TBI conditioning regimens [6, 17].

We gathered all the information about HSCT characteristics including donor type and selection, hematopoietic stem cell (HSC) sources, GFs and engraftment status, GvHD prophylaxis, and RRT. These findings are presented in Tables 2 and 3.

3.5 | Studies With Both MAC-TBI and MAC Non-TBI Conditioning Regimen

Three studies, including 44 patients (23 receiving TBI and 21 without TBI), described using both protocols. The patients' HSCT age ranged from 1.1 to 15.7 years (median age: 4.67 years), with a female-to-male ratio of 25:19.

MAC-TBI regimens in these articles consisted of cyclophosphamide (CY), cytarabine (Ara-C), BU, anti-lymphocyte globulin (ALG), TBI/thoracoabdominal irradiation (TAI) in eight patients [7]; CY, BU, total lymphoid irradiation (TLI), Ara-C, anti-thymocyte globulin (ATG) and TBI in 11 patients [16], and BU CY, FLU, ATG, melphalan (MEL), and TBI in four patients [15].

It is important to note that the last study's sample size encompassed 27 patients in total, of which 12 received the MAC regimen and 15 received the reduced intensity conditioning (RIC) regimen; only the 12 patients who underwent the MAC regimen were included in our study.

TABLE 1 | Baseline and characteristics of articles and overview of the systematic review.

Patient number	MAC-TBI	MAC non-TBI	OS (MAC-TBI)	OS (MAC non-TBI)
84	23	61	83%	85%

TABLE 2 | The patient and clinical characteristics of the cohorts concerning the group.

Study	Year of publish	Country	Pt/HSCT	Median age	F:M ratio
Ohga	2004	Japan	13/13	4.75 (1.25–11.33)	7:6
Fagioli	2014	Italy	30/31	6 (1.3–19.8)	13:17
Koyamaishi	2020	EBMT	12/12	3.6 (1.1–11.7)	3:9
Mugishima	2017	Japan	19/21	4.67 (1.25–15.67)	9:10
Behfar	2019	Iran	10/10	6.7 (2–15)	1:9

Abbreviations: F, female; M, male.

TABLE 3 | The HSCT characteristics of the cohorts concerning the group.

Study	GvHD prophylaxis (*n*)	Donor type	SC source	Conditioning regimen	HLA-matching.
Ohga	CsA+ALG (1) CsA+MTX (4) CsA (4) CsA+MTX+ALG (2) CsA+PSL (1) FK506 (1)	MSD: 6 MUD: 3 MMUD: 4	BM: 9 CB: 4	CY/ALG/ATG BUS/Ara-C	Full-matched: 9 MM: 4
Fagioli	CsA-based regimen in majority of patients	MSD: 16 MUD: 14	BM: 21 BM+CB: 5 PB: 1 CB: 3	BU/TT/FLU/TREO/ CY/L-PAM	Full-matched: 30
Koyamaishi	MTX+TAC (8) MTX+CsA (2) TAC (1) CsA, mPSL (1)	MSD: 3 MUD: 5 MMUD: 4	BM: 13	BU (7.6–19.2 mg/kg) CY (100–200 mg/kg) ATG (2.5–5 mg/kg) FLU (100–180 mg/m^2) TAI/TBI/TLI = 3 Gy	Full-matched: 8 MM: 4
Mugishima	CsA+MTX+ATG (3) CsA+MTX (5) CsA (4) CsA+ATG (2) MTX (1) FK (2) FK+MTX (2)	MSD: 8 MUD: 6 MMUD: 4 MMRD: 1	BM: 13 PB: 1 CB: 5	CY (60–200 mg/kg) BU (8–20 mg/kg) ATG (10–60 mg/kg) FLU (150 mg/m^2) Ara-C (12 g/m^2) TBI/TAI/TLI (3.5–12 Gy)	Full-matched: 14 MM: 5
Behfar	Cyclosporine A (CsA; 1.5 mg/kg daily, IV starting on Day −1 and then increased to 3 mg/kg from Day +7 for PBSC recipients or Day +11 for BMSC and CBSC recipients) plus a short course of methotrexate (10 mg/m^2 on Day +1 and 6 mg/m^2 on Days +3 and +6 except for CBSC recipients)	MSD: 8 MRD (mother): 1 MUD: 1	BM: 2 CB: 2 PB: 6	BU (1 mg/kg/q.i.d. for <9 kg, 1.2 mg/kg/q.i.d. for 9 to <16 kg, and 1.1 mg/kg/q.i.d. for 16–23 kg) for 4 consecutive days/CY (50 mg/kg for 4 consecutive days) ATG (2.5 mg/kg/day in 3 consecutive days)	Full-matched: 10

Abbreviations: ATG, anti-thymocyte globulin; BM, bone marrow; BU, busulfan; CB, cord blood; CS, corticosteroid; CsA, cyclosporine A; CY, cyclophosphamide; FK, FK506/tacrolimus; FLU, fludarabine; GF, graft failure; HID, haploidentical donor; HLA, human leukocyte antigen; L-PAM, L-phenylalanine mustard; MD, matched donor; MMD, mismatched donor; MMF, mycophenolate mofetil; MMUD, mismatched unrelated donor; mPSL, methylprednisolone; MTX, methotrexate; PB, peripheral blood; q.i.d., four times a day; R, related; S, sibling; SC, stem cell; Tac, tacrolimus; TCD, T-cell depletion; U, unrelated; XRT, radiation therapy.

TABLE 4 | The primary HSCT outcomes of the cohorts concerning the conditioning regimen protocol group.

Study	Acute GvHD	Chronic GvHD	Engraftment status	Serious adverse effects
Ohga	TBI: 5 Non-TBI: 1	No available data	1 patient with secondary graft failure	TBI group: 1 death occurred due to Epstein–Barr virus-associated lymphoproliferative disease
Fagioli	Non-TBI: 17	Non-TBI: 5	1 patient with primary graft failure/1 death due to VOD	VOD and extensive cGvHD
Koyamaishi	TBI: 3 Non-TBI: 8	Non-TBI: 3	1 patient with secondary graft failure	Pulmonary edema, SOS, ES, PCI, paralytic ileus, delayed platelet recovery, PRES, acute pancreatitis, HC, TMA
Mugishima	TBI: 9 Non-TBI: 4	TBI: 3 Non-TBI: 1	2 patients experienced primary graft failure in TBI group and 1 patient in non-TBI group	Non-TBI group: pulmonary bleeding and sepsis ($n = 1$) TBI EBV-associated lymphoproliferative disease ($n = 1$)
Behfar	Non-TBI: 8	Non-TBI: 1	1 patient had primary graft failure	Acute GvHD Grade III–IV ($n = 2$) and graft failure ($n = 1$)

Abbreviations: aGvHD, acute GvHD; cGvHD, chronic GvHD; ES, engraftment syndrome; HC, hemorrhagic cystitis; PCI, pneumatosis cystoides intestinalis; PRES, posterior reversible encephalopathy; SOS, sinusoidal obstructive syndrome; TMA, thrombotic microangiopathy; VOD, veno-occlusive disease.

The MAC non-TBI regimens in these articles consisted of BU, CY, ATG, TLI, MEL, and FLU in eight patients [15], CY, Ara-C, BU, and ATG in eight patients [16], and CY, BU, Ara-C, TLI, and ALG in five patients [7].

3.6 | Studies With MAC Non-TBI

As previously mentioned, two studies [6, 17] within the current analysis did not utilize TBI in their respective cohorts. These two studies comprised 40 patients who underwent HSCT without TBI. The age at HSCT ranged from 1.3 to 19.8 years (median of medians: 6.35 years), with a female-to-male ratio of 14:26. The MAC regimen used in one study [17] consisted of busulfan (BU), treosulfan (TREO), cyclophosphamide (CY), thiotepa (TT), and fludarabine (FLU). The other study [6] utilized BU and CY with or without anti-thymocyte globulin (ATG).

3.7 | Engraftment and Graft Failure

Of the 23 patients who received MAC-TBI regimen, four experienced GF, with two instances of primary GF and two secondary GF [7, 15, 16]. Three of the 61 patients who received a MAC non-TBI regimen developed primary GF. The incidence of both primary and secondary GF was higher in the MAC-TBI group (17%) compared to the MAC non-TBI group (5%), with reported ranges of 12.5%–25% versus 0%–10%, respectively [6, 7, 15–17].

A 2020 cohort study reported successful stem cell transplant in 12 DBA patients using a MAC regimen (four MAC-TBI and eight MAC non-TBI). One patient in the TBI group developed secondary GF 24 months post-HSCT [15]. An Iranian cohort of 10 DBA patients undergoing HSCT with a MAC non-TBI regimen reported only one instance of primary GF, achieving a 90% engraftment rate [6]. Fagioli et al. reported 28 successful DBA transplantations using a MAC non-TBI protocol, with one patient experiencing primary GF. In this cohort, one patient died immediately post-HSCT due to veno-occlusive disease (VOD) and achieved neither neutrophil nor platelet engraftment [17]. A Japanese cohort of 19 pediatric DBA patients undergoing HSCT (11 with MAC-TBI and eight with MAC non-TBI) reported primary GF in two patients in the MAC-TBI group and one in the MAC non-TBI group, corresponding to engraftment rates of 81% and 87.5%, respectively [16]. In a study by Ohga et al., 12 patients achieved effective engraftment, and one patient in the MAC-TBI group experienced secondary GF 7 months post-HSCT, representing engraftment rates of 87.5% and 100% in the MAC-TBI and MAC non-TBI groups, respectively [7].

3.8 | Acute and Chronic GvHD Incidence

The incidence of aGvHD was slightly higher in the MAC-TBI group compared to the MAC non-TBI group (74% vs. 62%). Conversely, cGvHD was more prevalent in the MAC non-TBI group (13% vs. 16%). A cohort study of 27 DBA patients, 12 of whom received a MAC regimen (four with TBI/TAI and eight without TBI), reported Grade II and III aGvHD in three patients in the TBI-MAC group. In the MAC non-TBI group, all eight patients developed aGvHD: four with Grade I (50%), three with Grade II (37.5%), and one with Grade III (12.5%). cGvHD was observed only in the MAC non-TBI group, affecting three patients in total (37.5%) [15].

In a 10-patient Iranian cohort (MAC non-TBI), Grade I–II aGvHD was reported in five patients (56%), and Grade III–IV aGvHD in two (22%). One patient developed cGvHD; no cGvHD was reported in the MAC-TBI group [6].

A Japanese cohort of 19 DBA patients (11 MAC-TBI, eight MAC non-TBI) reported Grade I–II aGvHD in six (55%) and Grade

III aGvHD in one (9%) patient in the MAC-TBI group. In the non-TBI group, Grade I–II aGvHD was seen in two (25%) patients and Grade III in one (12.5%). No cGvHD was reported in the MAC non-TBI group, while one patient (9%) in the MAC-TBI group developed cGvHD [16]. In another Japanese cohort (13 patients, eight MAC-TBI, five MAC non-TBI), one MAC-TBI patient died and another experienced graft rejection. Five patients in this group developed aGvHD. In the MAC non-TBI group, one patient (20%) developed Grade I–II aGvHD. No data on cGvHD incidence were provided in this study [7].

A report from the Italian Association of Pediatric Hematology and Oncology Registry, involving 30 patients (all MAC non-TBI), reported Grade I–II aGvHD in 10 (33%) patients and Grade III–IV aGvHD in seven (23%). Five patients (17%) developed cGvHD [17].

3.9 | Severe Adverse Events

Overall, SAEs were observed more frequently in MAC non-TBI group. Types of SAEs in the two groups were different; however, EBV-associated lymphoproliferative disease (EBV-LPD) was reported in both MAC-TBI and MAC non-TBI patients.

Among 61 patients who underwent HSCT using MAC non-TBI conditioning regimen, the most common SAE was thrombotic microangiopathy (TMA), which was reported in three patients (4.9%). Acute pancreatitis and VOD were reported with the same prevalence; each in two patients (prevalence: 3.2%). Other complications, including pulmonary edema, sinusoidal obstructive syndrome (SOS), engraftment syndrome (ES), paralytic ileus, delayed platelet recovery, posterior reversible encephalopathy (PRES), hemorrhagic cystitis (HC), sepsis, CMV antigenemia (CMV-Ag), EBV-LPD, and pulmonary hemorrhage, were only reported in one patient in each study.

In the MAC-TBI group, complications such as EBV-LPD, pulmonary bleeding, sepsis, and TMA were reported in two patients (8.6%). Pneumatosis cystoides intestinalis (PCI), pancreatic ileus, and VOD were other complications that, respectively, affected one patient in each study (4.3%) [7, 15, 16].

Fagioli. et al. reported malignant osteosarcoma (Grade 3) in one DBA patient 10 years after HSCT using MAC non-TBI protocol [17].

3.10 | Overall Survival Rate

Studies have suggested a slightly higher OS rate in patients undergoing HSCT with a MAC non-TBI regimen compared to those receiving a MAC-TBI protocol (85% vs. 82%, respectively).

In a cohort study by Mugishima et al. [16], 11 patients (58%) received cyclophosphamide (CY) with irradiation (nine TBI and two total abdominal irradiation [TAI]), while eight patients (42%) received CY without irradiation. Patients receiving total lymphoid irradiation (TLI) were excluded from this analysis due to procedural differences. One death, attributed to pulmonary bleeding and sepsis, occurred in the MAC non-TBI group. Three deaths were reported in the MAC-TBI group, including one due to EBV-associated lymphoproliferative disease (EBV-LPD). Data regarding the causes of the two other deaths in the MAC-TBI group were not available. The 5-year OS was slightly higher in the MAC non-TBI group (87.5%) compared to the MAC-TBI group (73%) [16].

In a cohort by Fagioli et al., patients received a CSA-containing GvHD prophylaxis regimen. The median dose of transplanted nucleated cells was 5×10^8 and 3×10^7 per kg recipient bodyweight for bone marrow (BM) and CB transplants, respectively. Per the study, VOD and extensive cGvHD contributed to mortality; however, no detailed data were published. In conclusion, 5-year OS was 74.4% among 30 patients [17].

In a cohort managed by Behfar et al., all patients received a MAC regimen based on BU and CY with or without ATG. BU was administered intravenously (IV); doses were adjusted according to the patient's weight (i.e., 1 mg/kg four times a day for dose of 2.5 mg/kg/day from Days −5 to −2).

One occurrence of graft rejection was noted, and two patients succumbed to Grade III–IV acute GvHD. Seven out of 10 (70%) patients experienced a 5-year survival [6].

In a cohort by Ohga et al., all patients received a CY-based MAC regimen, five patients received BU, seven patients received ALG, and one patient received an additional Ara-C. GvHD prophylaxis included cyclosporine (CsA) in all patients, methotrexate (MTX) (six patients) and ALG (three patients). One death was reported in the MAC-TBI group because of EBV-LPD, which elucidates an 87.5% survival rate. All patients (100%) receiving MAC non-TBI regimen survived in this study [7].

In a 2020 cohort directed by Koyamaishi et al., the MAC regimen included BU, CY, and immunosuppressive agents including ATG (2.5–5 mg/kg), FLU (100 mg/m^2), and MEL (140 mg/m^2). In this study, eight patients received a GvHD prophylaxis regimen based on MTX and TAC, two received MTX and CsA, one received TAC only, and another one only CsA and methylprednisolone (mPSL). Three-year survival rate was reported 100% in both MAC-TBI and MAC non-TBI receiving patients [15].

3.11 | Effect of Age at HSCT on Post-Transplant Complications

At first, we attempted to perform a meta-analysis on how age affected post-HSCT complications, but due to heterogeneity of data and variable conditioning/prophylaxis regimens, it was not possible to divide patients into equal subgroups and case and control arms. Nevertheless, instead of analyzing the whole sample size, we compared the adverse events and survival rates in several small groups of patients in which the same conditioning regimens had been used. As expected, under the same circumstances, lower age at the time of HSCT was correlated with lower adverse events and better survival rates.

In the cohort managed by Fagioli et al., the median age of all patients at the time of HSCT was 6 years. Two patients received a radiation-free conditioning regimen based on BU, TT, and FLU. At the time of HSCT, one patient was 2 years old and the other was 14.3 years old; the 2-year-old patient survived, but the older

patient expired due to extensive cGvHD; further detail was not given in the article. In this study, a conditioning regimen based on TREO, TT, and FLU was used in two patients who were 7.8 and 16.7 years old. Similarly, the younger patient survived the procedure, but the older patient died due to an SAE after HSCT [17].

In the Japanese cohort study conducted by Ohga et al., a conditioning regimen based on TBI, ALG, and CY was used in two patients; the older patient was 7.7 years old when he received HSCT, and the other patient was of 4.2 years. No adverse events or mortality were reported for the younger patient; conversely, the older patient developed Grade II aGvHD.

Although a regimen based on PSL and CsA was used in all five patients aged 1.3, 2.6, 2.8, 6.5, and 8 years at the time of HSCT, the two older patients manifested the signs of Grade I aGvHD, but three younger patients remained unaffected despite the similar regimen [7].

Behfar et al. treated 10 DBA patients using radiation-free MAC regimen mainly based on BU and CY; the median HSCT age among these patients was 6.7. Two patients died due to Grade III–IV aGvHD,; these two patients were 13 and 15 years old. Considering the median HSCT age and the similar regimen used in almost all patients, post-HSCT mortality is observed more frequently among patients with a higher age [6].

In the two remaining articles by Koyamaishi et al. and Mugishima et al., different conditioning and prophylaxis regimens were used in almost all patients; and thus, appropriate comparison based on HSCT outcomes and age was not possible. However, if minutia was ignored and outcomes were generally compared, the lower HSCT age was related to better outcomes [15, 16].

3.12 | Donor and Stem Cell Source

Sufficient data have been gathered to elucidate the impact of high-resolution HLA-typing on HSCT outcomes. Evidently, patients with MSDs reported less aGvHD, cGvHD, and mortality risk. All studies under review unanimously corroborated these findings.

These studies used three main stem cell sources: bone marrow (BM), peripheral blood (PB), and cord blood (CB). However, the variability and heterogeneity in patient numbers, transplant factors, and conditioning regimens made it difficult to draw clear conclusions. Some studies reported better results using BM as graft source. CB or PB stem cells were reported to cause less severe immune responses and cell toxicities. Due to the method of allocation and statistical analysis, the role of confounders could not be ignored.

3.13 | Meta-Analysis

For each study, the central box on the forest plot represents the point estimate (risk ratio), and the horizontal line represents the 95% confidence interval (CI). The diamond represents the pooled risk ratio and confidence interval.

4 | Discussion

This systematic review was first designed to compare the efficacy of MAC regimens versus RIC regimens in HSCT, hypothesizing that RIC regimens, with their lower toxicity profile, could improve HSCT outcomes. While MAC regimens have been extensively studied in DBA patients, the application of RIC regimens has been limited, primarily documented in small case reports, case series, or conference proceedings with insufficient sample sizes [5, 15, 18–21]. Although some studies utilizing RIC regimens with over 10 patients exist, the aggregate data remain insufficient for robust analysis, underscoring the need for further research to evaluate this promising protocol and facilitate comprehensive systematic reviews.

The rarity of DBA posed a notable challenge in determining methodologically and statistically valid studies. Many studies lacked comprehensive data reporting, including precise OS stratified by years and months, progression-free survival rates, DFS rates, and SAEs for individual patients. One study [7] failed to report comprehensive data on cGvHD, a critical outcome measure in comparing these conditioning regimens.

This systematic review represents the first attempt at a rigorous analysis of the impact of TBI within MAC regimens on HSCT outcomes. To ensure transparency and minimize bias, the research question was prospectively defined, and a systematic search and selection methodology was employed. However, several limitations were encountered. Incomplete reporting of key variables, including patient age, disease status and subtype, specific conditioning regimen protocols, irradiation types, and HSCT outcomes, limited the scope of definitive conclusions. While broadening the inclusion criteria could have addressed some of these limitations and improved cohort comparability, this was not done in the current study.

The findings indicate a trend toward higher mortality and lower survival rates in the MAC-TBI group compared to the MAC non-TBI group, albeit these differences were not statistically significant. The incidence of both primary and secondary GF was higher in the MAC-TBI group. While aGvHD was slightly more prevalent in the MAC-TBI group, cGvHD was more common in the MAC non-TBI group. Despite the numerous existing cohorts examining the effects of different conditioning regimens on HSCT outcomes, the available evidence remains limited due to significant heterogeneity and methodological inconsistencies across studies. Further high-quality research is needed to address these limitations and provide more definitive conclusions.

Author Contributions

Parsa Fathi: Data collection and scientific writing. Leila Jafari: editing and data collection. Ayat Ahmadi: meta-analysis and statistical assessment. Yalda Karamlou: editing. Maryam Behfar: data validation. Amir Ali Hamidieh and Afshin Fathi: supervision and guidance.

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Clinical Trial Registration

The authors have confirmed clinical trial registration is not needed for this submission.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.