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ORIGINAL RESEARCH REPORT

Efficacy of Allogeneic Hematopoietic Cell Transplantation in Patients With Chronic Phase CML Resistant or Intolerant to Tyrosine Kinase Inhibitors

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Abstract

Approximately 15−20% of chronic myeloid leukemia (CML) patients fail tyrosine kinase inhibitor (TKI) therapy secondary to resistance or intolerance. In the pre-TKI era, front-line allogeneic hematopoietic cell transplantation (allo-HCT) represented the standard approach for patients with chronic phase-CML (CP-CML) who were deemed fit to tolerate the procedure and had a human leukocyte antigen compatible donor available. Currently, CP-CML patients are eligible for allo-HCT only if they fail more than one TKI and/or are intolerant to the drug. We performed a systematic review/meta-analysis of the available literature to assess the evidence regarding allo-HCT efficacy in CP-CML patients. Data from eligible studies were extracted in relation to benefits (overall survival [OS], progression-free survival, disease-free survival [DFS], complete remission [CR], and molecular response [MR]) and harms (nonrelapse mortality [NRM], relapse, and acute and chronic graft-versus-host disease), and stratified by age into adult and pediatric groups. For adult allo-HCT recipients, the pooled OS, DFS, CR and, MR were 84% [95% confidence interval (CI) 59−99%], 66% (95% CI 59−73%), 56% (95% CI 30−80%), and 88% (95% CI 62−98%), respectively. Pooled NRM and relapse were 20% (95% CI 15−26%) and 19% (95% CI 10−28%), respectively. For the pediatric group, the OS rate was reported in one study and was 91% (95% CI 72−99%). Our results suggest that allo-HCT is an effective treatment for TKI-resistant or TKI-intolerant CP-CML. Post-transplant strategies are still needed to further mitigate the risk of relapse.

Keywords: Allogeneic hematopoietic cell transplantation, Chronic myeloid leukemia, Chronic phase, Intolerance, Resistance, Tyrosine kinase inhibitors

1. Introduction

Incorporation of tyrosine kinase inhibitors (TKIs) into the treatment algorithm of chronic myeloid leukemia (CML) in chronic phase (CP) marked the beginning of a new era that largely replaced the use of allogeneic hematopoietic cell transplantation (allo-HCT) in the front-line setting [1]. Two decades later, allo-HCT, *albeit* relegated to a salvage therapy following TKI resistance or intolerance, remains a reasonable option for CP-CML. It is estimated that approximately 15−20% of patients would fail TKI therapy secondary to resistance or intolerance [2]. The European Leukemia Network recommends allo-HCT to be considered for patients who are resistant or intolerant to at least one of the second-generation TKIs [3].

Conducted in the TKI era, the German CML study IV reported outcomes of 84 patients who underwent allo-HCT after imatinib failure or due to advanced disease: the 3-year survival for 56 patients who were allografted in CP was 91%, whereas it was 59% for those in advanced phase. Nonrelapse mortality (NRM) was estimated at 8% for patients who received

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an allo-HCT in CP compared with 18% for those transplanted at later stages [4]. Another study from a Swedish registry reported outcomes of 118 patients (47.5% in CP) who underwent allo-HCT for CML between 2002 and 2017. In this study, TKI resistance was the most common indication for allo-HCT (62.5%). The 5-year overall survival (OS) was 96.2%, 70.1%, and 36.9% for patients in CP1, CP2/>CP2, and advanced phase/blast phase, respectively [5].

In the absence of a randomized controlled study for TKI-resistant and/or TKI-intolerant CP-CML that compares allo-HCT with other available therapies, we perform a systematic review/meta-analysis (SR/MA) of the available literature to assess the totality of evidence regarding the efficacy of allo-HCT in patients with TKI-resistant CP-CML.

2. Methods

2.1. Search and selection of eligible studies

We followed the recommendations by the Cochrane Collaboration for the minimum number of databases to be searched (i.e. $n = 2$). According to a predefined protocol, a comprehensive search of the published medical literature was undertaken using two major databases, namely, PubMed/MEDLINE and Embase on January 24, 2020 (Appendix 1). In addition, we performed a manual search of cited references from relevant narrative review articles to identify additional eligible studies. We did not apply any search limits based on country of origin, date of study conduct, or study setting (prospective, retrospective from a single center or multiple centers, or registry data), but excluded studies that were not in English or only reported in abstract form.

Eligibility for inclusion in this SR/MA required that studies must have enrolled 10 or more patients who received an allo-HCT for treating CP-CML that was either TKI resistant or intolerant. Selection of included studies was undertaken by two authors (F.Y. and M.A.K-D). Possible disagreements were resolved by consensus majority in consultation with two separate coauthors (T.R. and A.K.).

2.2. Data collection

All authors extracted data from included studies using a standardized data collection form. We collected data on study and participant characteristics, clinical outcomes based on benefits ([OS], progression-free survival [PFS], disease-free survival [DFS], complete remission [CR], and molecular response [MR]) and harms (NRM, relapse, and acute [aGVHD] and chronic [cGVHD] graft-versus-host disease), and the risk of bias. All outcomes were stratified by age group into adults (median age and lower limit of age range $\geq$ 18 years) and pediatrics (defined as median age and upper limit of age range < 18 years). Studies which had an overlap of these age cut-offs were grouped under the label of mixed/unclear population.

The methodologic quality of eligible studies was assessed using the Newcastle–Ottawa Scale modified for single-arm cohort studies [6].

2.3. Statistical analysis

In this SR/MA, we calculated proportions for each specific outcome of interest. For the MA, the proportions were transformed into quantities according to the Freeman–Tukey variant of the arcsine square root-transformed proportion [7,8]. The pooled proportion was calculated as the back-transformation of the weighted mean of the transformed proportions using the random-effects model proposed by DerSimonian and Laird [7], which was used to pool data from studies with similar definitions pertaining to study design, study patients, and allo-HCT outcomes. All results are reported as rates with their corresponding 95% confidence intervals (CIs).

2.4. Analysis of heterogeneity

For pooled outcomes with data from four or more studies, we assessed heterogeneity among the studies included in this SR/MA using the I^2 statistic as described by Higgins et al. [9]. Moderate heterogeneity was defined as $I^2 > 30\%$, and high heterogeneity was defined as $I^2 > 60\%$. All analyses reported in this SR/MA were performed by Stata version 16 software (StataCorp LLC, College Station, TX, USA) and the MetapropOne software package (StataCorp LLC, College Station, TX, USA) [10]. The review is reported in accordance with PRISMA guidelines [11].

3. Results

3.1. Search results

Our search strategy (Appendix 1) identified a total of 1308 studies. Only nine studies ($n = 439$ patients) met our inclusion criteria [4,12–19]. Stratification by age group yielded three studies ($n = 200$ patients) in the adult, one study ($n = 28$ patients) in the pediatric, and five studies ($n = 211$ patients) in the mixed population. The three most common reasons for exclusion were (a) not a clinical study, (b) not CML diagnosis, and (c) not allo-HCT (Fig. 1).

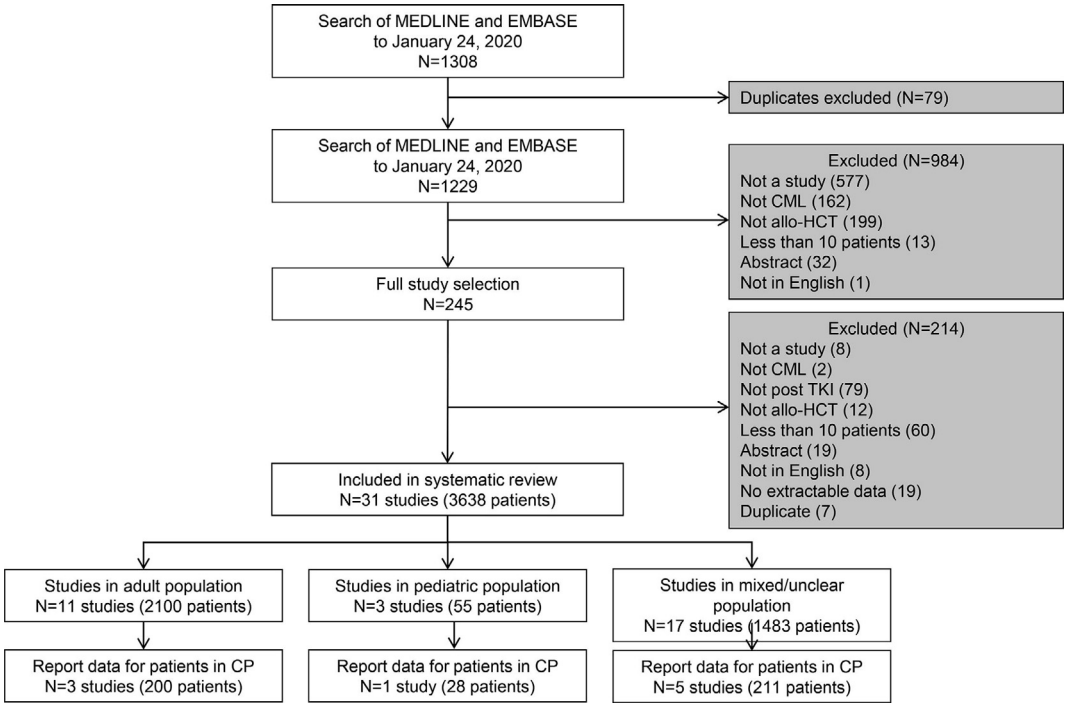

Fig. 1. Study selection flow diagram. Note. CP = chronic phase; allo-HCT = allogeneic hematopoietic cell transplantation; TKI = tyrosine kinase inhibitor.

3.2. Characteristics of included studies

Table 1 summarizes the characteristics of the studies included in this SR/MA.

3.3. Assessment of methodological quality of selected studies

Table 2 summarizes the methodologic quality and risk of bias of the studies included in this SR/MA. Three studies represented multiple institution data [4,15,16] and three were registry studies [14,18,19]. In brief, the majority of the included studies were classified as low/relatively low risk in terms of selection bias (for including a representative sample, ascertainment of exposure, and baseline diagnosis) and outcome bias (for assessment methods and adequate follow-up).

3.4. Outcomes

3.4.1. OS

3.4.1.1. Adult. OS was reported in three studies ($n = 187$) [12–14]. The pooled OS rate was 84% (95% CI 59–99%). Heterogeneity was nonassessable (Fig. 2).

3.4.1.2. Pediatric. OS was reported in one study ($n = 23$) [15]. The OS rate was 91% (95% CI 72–99%; Fig. 2).

3.4.1.3. Mixed/unclear population. OS was reported in four studies ($n = 164$) [4,17–19]. The pooled OS was 76% (95% CI 56–92%). Heterogeneity was high ($I^2 = 86.4\%$, $p < .001$; Fig. 2).

3.4.2. PFS

3.4.2.1. Mixed/unclear population. The PFS rate was reported in one study ($n = 11$) [17] and it was 82% (95% CI 48–98%; Appendix 1, Figure a).

3.4.3. DFS

3.4.3.1. Adult. The DFS rate was reported in three studies ($n = 186$) [12–14]. The pooled DFS rate was 66% (95% CI 59–73%). Heterogeneity was nonassessable (Appendix 1, Figure b).

3.4.3.2. Mixed/unclear population. The DFS rate was reported in two studies ($n = 97$) [16,18]. The pooled

Table 1. Post-transplant outcomes of eligible studies.

Study	Study type	N1	N2	Median age (range), years	OS, % PFS, % DFS, %	CR, % MR, %	NRM, %	Relapse, %	aGVHD, % cGVHD, %
Adults									
Jabbour et al. [12]	Single center	47	16	44 (19–63)	OS: 75 (2 y) PFS: NE DFS: 63	CR: 56 MR: 88	19 (2 y)	25	NE
Nair et al. [13]	Single center	51	17	45 (22–61)	OS: 100 (8 y) PFS: NE DFS: 71 (8 y)	NE	20 (1–5 y)	29 (1–5 years)	NE
Kondo et al. [14]	TRUMP registry	237	154	42 (20–67)	OS: 70 (2 y) PFS: NE DFS: 65 (2 y)	NE	21 (2 y)	16 (2 years)	NE
Pediatric									
Suttorp et al. [15]	Multicenter	28	23	13.2 (1.3–18)	OS: 91 (5 y) PFS: NE DFS: NE	NE	NE	NE	NE
Mixed/unclear									
Bornhäuser et al. [16]	Multicenter	61	47	45 (15–64)	OS: NE PFS: NE DFS: 34 (18 mo)	NE	49 (100 d to 1 y)	26 (18 months)	NE
Perz et al. [17]	Single center	37	19	31 (16–55)	OS: 68 PFS: 82 DFS: NE Median follow-up: 203 d	NE	12 (100 d)	NE	NE
Saussele et al. [4]	Multicenter	1,242	37	38 (16–56)	OS: 95 (3 y) PFS: NE DFS: NE	CR: NE MR: 89	NE	NE	aGVHD: 68 cGVHD: 35
Lee et al. [18]	CIBMTR registry	1,309	50	33 (14–54)	OS: 80 (4 y) PFS: NE DFS: 60 (4 y)	NE	NE	28 (4 years)	aGVHD: 46 cGVHD: 63
Kruger et al. [19]	ABMTR registry	80	58	40 (17–63)	OS: 55 (5 y) PFS: NE DFS: NE	NE	NE	NE	NE

Note. ABMTR = Australasian Bone Marrow Transplant Recipient; aGVHD = acute graft-versus-host disease; cGVHD = chronic graft-versus-host disease; CIBMTR = The Center for International Blood & Marrow Transplant Research; CML = chronic myeloid leukemia; CR = complete remission; d = day; DFS = disease-free survival; F/U = follow-up; mo = month; MR = molecular response; N1 = number of patients enrolled in the study; N2 = number of patients included in the analysis; NE = non-extractable data; NRM = non-relapse mortality; OS = overall survival; PFS = progression-free survival; TRUMP = Transplant Registry Unified Management Program; y = year.

Table 2. Risk of bias in included studies.

Study	Representativeness of the patient cohort	Ascertainment of exposure	Demonstration that the outcome of interest was not present at the start of study	Assessment of outcome	Length of follow-up	Adequacy of follow-up
Adults						
Jabbour et al. [12]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Nair et al. [13]	Unclear/high risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kondo et al. [14]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Pediatric						
Suttorp et al. [15]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Mixed/unclear						
Bornhäuser et al. [16]	Low risk	Low risk	Low risk	Low risk	Unclear/high risk	Low risk
Perz et al. [17]	Unclear/high risk	Low risk	Low risk	Low risk	Unclear/high risk	Low risk
Saussele et al. [4]	Low risk	Unclear/high risk	Low risk	Low risk	Low risk	Low risk
Lee et al. [18]	Unclear/high risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kruger et al. [19]	Unclear/high risk	Low risk	Low risk	Low risk	Low risk	Low risk

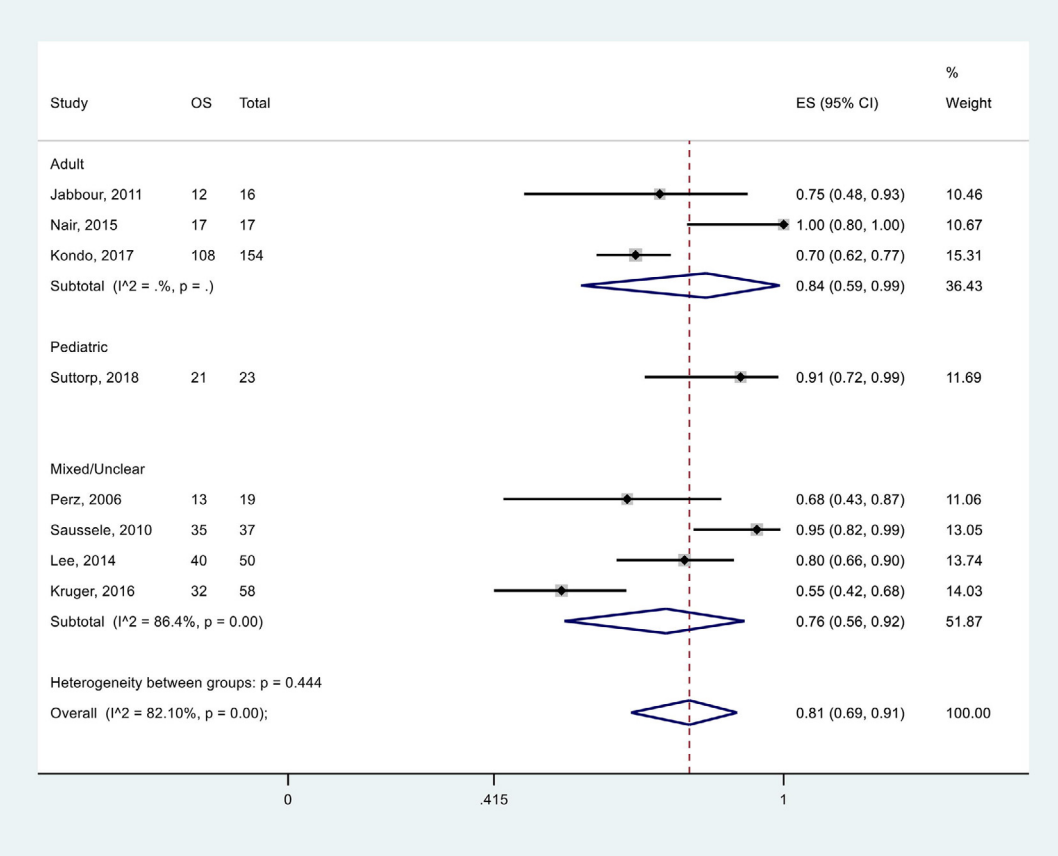

Fig. 2. Overall survival (OS). Note. CI = confidence interval; ES = effect size.

DFS was 47% (95% CI 37–57%; Appendix 1, Figure b).

3.4.4. CR

3.4.4.1. Adult. The CR rate was reported in one study (n = 16) [12] and was 56% (95% CI 30–80%; Appendix 1, Figure c).

3.4.5. MR

3.4.5.1. Adult. The MR rate was reported in one study (n = 16) [12] and was 88% (95% CI 62–98%; Appendix 1, Figure d).

3.4.5.2. Mixed/unclear population. The MR rate was reported in one study (n = 28) [4] and was 89% (95% CI 72–98%; Appendix 1, Figure d).

3.4.6. NRM

3.4.6.1. Adult. NRM was reported in three studies (n = 199) [12–14]. The pooled NRM rate was 20% (95% CI 15–26%). Heterogeneity was nonassessable (Fig. 3).

3.4.6.2. Mixed/unclear population. NRM was reported in two studies (n = 97) [16,18]. The pooled NRM was 28% (95% CI 19–38%; Fig. 3).

3.4.7. Relapse

3.4.7.1. Adult. Relapse was reported in three studies (n = 187) [12–14]. The pooled relapse rate was 19% (95% CI 10–28%). Heterogeneity was nonassessable (Fig. 4).

3.4.7.2. Mixed/unclear population. Relapse was reported in two studies (n = 97) [16,18]. The pooled relapse was 27% (95% CI 18–36%; Fig. 4).

3.4.8. aGVHD

3.4.8.1. Mixed/unclear population. aGVHD was reported in two studies (n = 87) [4,18]. The pooled

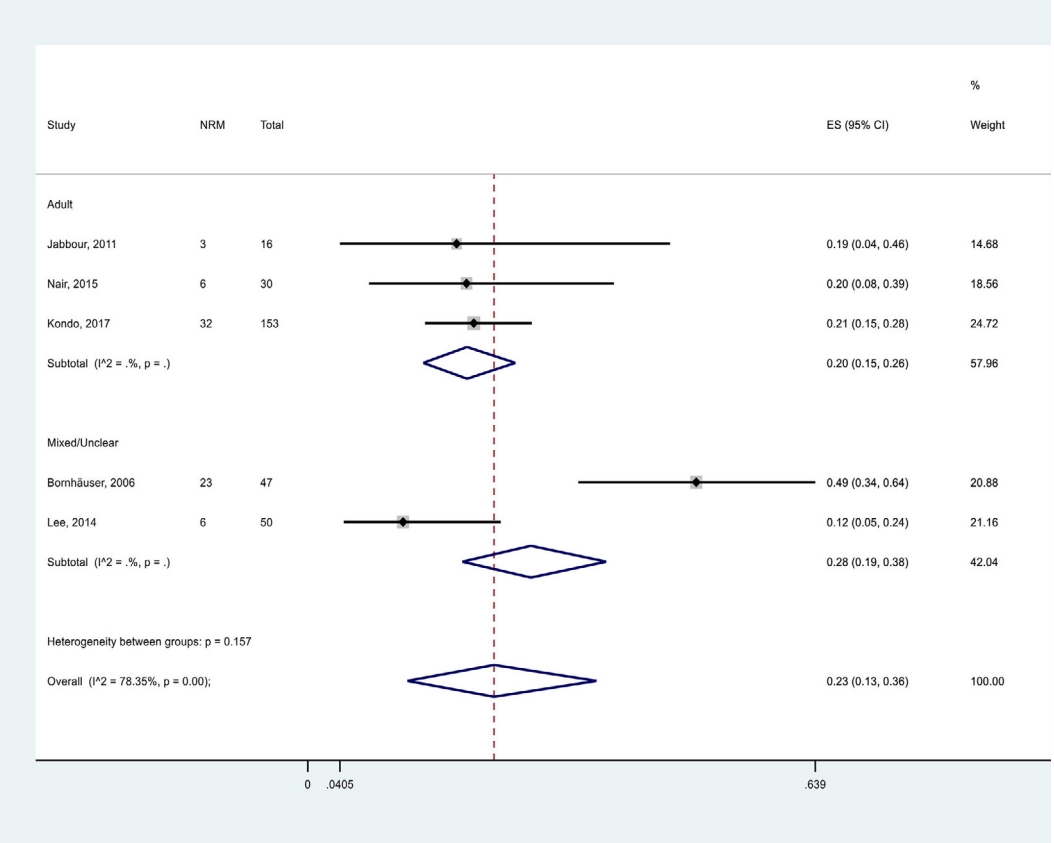

Fig. 3. Nonrelapse mortality (NRM). Note. CI = confidence interval; ES = effect size.

aGVHD was 46% (95% CI 35–56%; Appendix 1, Figure e).

3.4.9. cGVHD

3.4.9.1. Mixed/unclear population. cGVHD was reported in two studies (n = 83) [4,18]. The pooled cGVHD was 51% (95% CI 40–61%; Appendix 1, Figure f).

4. Discussion

In the pre-TKI era, front-line allo-HCT represented the standard approach for patients with CP-CML who were deemed fit to tolerate the procedure and had a human leukocyte antigen compatible donor available. Following the emergence of imatinib mesylate, and later on newer generations of TKIs, the role of allo-HCT in CP-CML was relegated to later stages of the disease owing to both the high response rates and long duration of remission following TKI therapies [1,20–22]. Nowadays, patients with CP-CML are considered eligible for allo-HCT only if they fail to respond to more than one TKI and/or if they are unable to tolerate the drug. This is not the case for patients with accelerated or blastic phases of the disease for which allo-HCT ought to be offered as front-line consolidation.

Results of this SR/MA show that allo-HCT yields encouraging pooled OS rates of 84% in adults and 91% in the pediatric age group. These results are noteworthy when considering that refractoriness to TKIs probably represents a more aggressive disease when compared with CP-CML that used to be allografted in the past after demonstrating responses to inferior therapies such as interferon [23]. The effectiveness of allo-HCT highlights the need for an early referral to a transplant center, particularly in the subgroup of CML patients with TKI resistance conferred by acquired kinase domain mutations.

Pertaining to harms, results of our SR/MA highlight a pooled NRM and relapse rates of 20% and 19%, respectively, in the adult age group. This emphasizes the need to develop better selection criteria to reduce the NRM risk, and to implement post-transplant strategies that could help further mitigate the risk of relapse. Early intervention in patients with residual disease using donor lymphocyte infusion(s) and/or TKIs represents reasonable

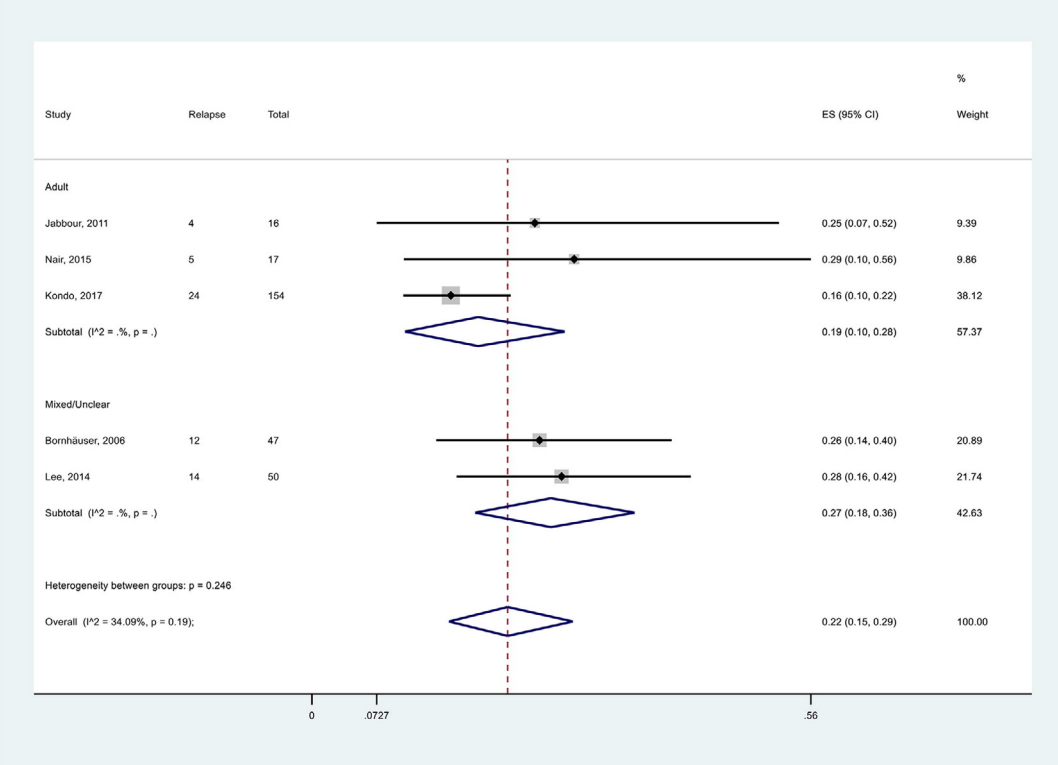

Fig. 4. Relapse. Note. CI = confidence interval; ES = effect size.

approaches in this setting considering the proven graft-versus-leukemia efficacy of donor lymphocyte infusion(s) in CML [24].

A major limitation of our study is the fact that outcomes based on regimen intensity were not extractable, as data were reported in aggregates rather than segregated into myeloablative versus reduced intensity regimens. Another limitation of our analysis is that we could not analyze the outcomes separately for patients allografted for TKI resistance versus those who received the procedure for TKI intolerance. Intuitively, the latter may represent a different disease biology for which resistance may have not been confirmed. Moreover, considering the retrospective nature of most studies, it is plausible that some may have an overlap of patients. This could be the case of patients reported in single-institution studies and in registry-based data. Finally, we acknowledge a limitation of not including studies published in abstract form only in our SR and MA. While including abstracts is recommended, a recently published scoping review of comparisons between abstracts and full reports in primary biomedical research showed that abstracts are frequently inconsistent with full reports [25]. Besides, our search only identified one eligible study in the pediatric age group.

Notwithstanding aforementioned limitations, our MA supports the need to develop future studies assessing novel maintenance/consolidation strategies to further reduce relapse following allo-HCT.

In conclusion, our results suggest that allo-HCT is an effective treatment strategy for CML patients who are resistant or intolerant to TKIs.

Declaration of Competing Interest

M.A.M. reports consultancy for Acrotech Biopharma and M.A.K-D reports consultancy for Pharmacyclics and Daiichi Sankyo. The other authors report no relevant conflicts of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hemonc.2021.02.003.

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