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Chronic graft-versus-host disease and the risk of primary disease relapse: A meta-analysis

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Both primary disease relapse (PDR) and chronic graft-versus-host disease (cGVHD) have long been the dreaded outcomes for patients with hematologic malignancies. Previous theories have speculated an inverse relationship between the two; therefore, we attempted to verify the described association. We searched for titles of articles in MEDLINE (PubMed), Cochrane library, and EMBASE database that evaluated the association between PDR and cGVHD and conducted a random effect meta-analysis of 11 studies involving a total of 64,239 participants. We found a significantly decreased risk of developing PDR in patients with cGVHD, with a pooled risk ratio of 0.49 (95% confidence interval: 0.40–0.61, $I^2 = 69.3\%$). We concluded that patients with cGVHD have a significantly lower risk of developing PDR compared with patients without cGVHD.

Primary disease relapse (PDR) and graft-versus-host disease (GVHD) have long been dreaded consequences of many malignant hematologic conditions. Active research is ongoing to further characterize and find effective methods to circumvent these complications.

GVHD is commonly divided into acute GVHD (aGVHD) and chronic GVHD (cGVHD), with a cutoff of 100 days per National Institutes of Health (NIH) consensus criteria [1]. On further exploration into its pathogenesis, cGVHD has been hypothesized to occur via complicated pathways involving host antigen presenting cells (APCs) and effector and regulatory T cells, as well as pro-inflammatory cytokines and co-stimulatory mediators [2,3] causing a constellation of clinical findings in various organs, most commonly involving the skin, alimentary tract, liver, and lungs [1,4]. As cGVHD is one of the most debilitating long-term consequences in the transplant era [5,6], circumventing this devastating side effect would prove to be a tremendous stride in the advancement of transplant medicine.

There are theories that try to explain the relationship between PDR and cGVHD. Falkenburg et al. [7] speculated that the graft-versus-tumor (GVT) effect is the primary mechanism underlying the prevention of PDR because of the strong alloreactivity from the T cells in the setting of allogenic stem cell transplant.

As human stem cell transplantation (HSCT) is being performed more frequently, the rate of cGVHD, as well as that of PDR, has increased because of both better detection technique and more widespread understanding of cGVHD and its manifestations. Therefore, we attempted to evaluate the association between cGVHD and PDR in the context of HSCT for malignant hematologic conditions.

Methods

We searched for titles of articles in MEDLINE (PubMed), the EMBASE database, and the Cochrane library. We performed a search in January 2019 and did not restrict publication dates. The main search terms used were hematopoietic stem cell transplant, hematologic malignancy, chronic graft-versus-host disease, and relapse. The full search strategy is detailed in Figure 1.

All published non-randomized trials that evaluated the outcome of cGVHD and PDR were included. Observational studies—prospective cohort, retrospective cohort, and cross-sectional studies—were included. Review articles, case reports, letters, commentaries, abstracts, unpublished studies, and studies in languages other than English were excluded.

Patient age, data sources, GVHD prophylaxis regimen, degree of HLA matching, and study location were not restricted. We included patients with all disease statuses as well as all conditioning regimens. Because of the various criteria for diagnosis of cGVHD and relapse, these data were not restricted. Studies done

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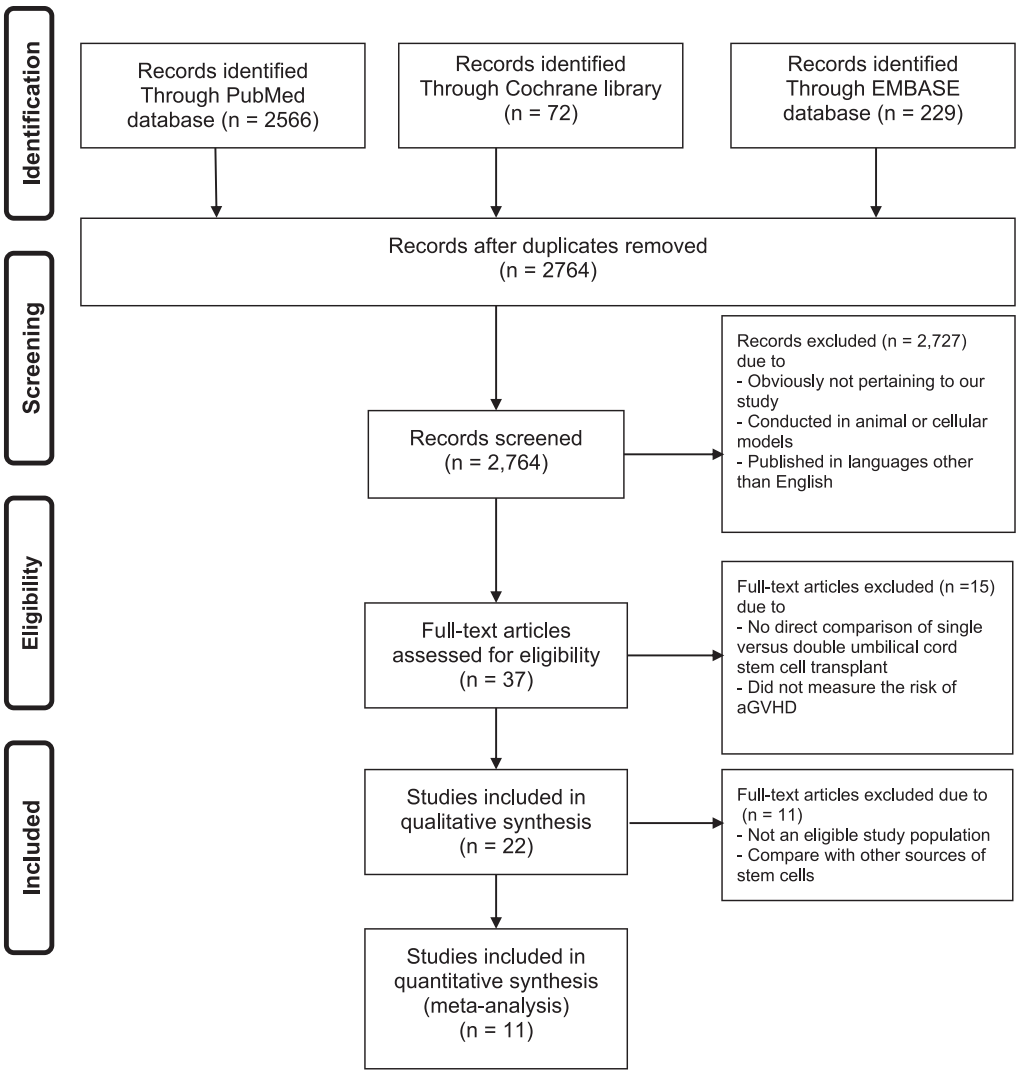

Figure 1. Search methodology and selection process.

in vitro or on animal models were excluded. We included only studies specific to hematologic malignancy patients who have undergone transplantation.

Our primary outcome was the relative incidences of cGVHD and PDR.

Data extraction and quality assessment

Two investigators independently extracted the following data: authors, publication year, country of origin, study design, baseline patient's characteristics, interventions, and outcomes. Any conflicting opinions on data extraction were resolved by consensus of the investigators.

The Newcastle–Ottawa Quality Assessment Scale (NOS) was used to assess the quality of the nonrandomized studies based on selection of the study groups, comparability of the study groups, and ascertainment of exposure/outcome. Studies with total scores >6 and <4 were considered to be of high and low quality, respectively. We excluded any studies indicated as poor quality by the meta-analysis. The studies were randomized according to each study's criteria but there were no blinded control trials.

Statistical methods

The primary outcome is the relative incidences of cGVHD and PDR. We used a random-effects model for our included studies, which were all retrospective observational studies. We conducted sensitivity analysis and subgroup analysis to explore the heterogeneity of the included studies [8]. We also used the funnel plot (Figure 2) and Egger's test to assess for publication bias. All analyses were performed using Stata 13 software at the 0.05 level of significance.

Results

Description of included studies

The initial search yielded 2,764 articles; 2,727 were excluded from the title and abstract review as they did not pertain to our study, had been conducted in animal or in vitro models, or were published in languages other than English (Table 1). A total of 37 articles underwent full-length review; 26 of them were

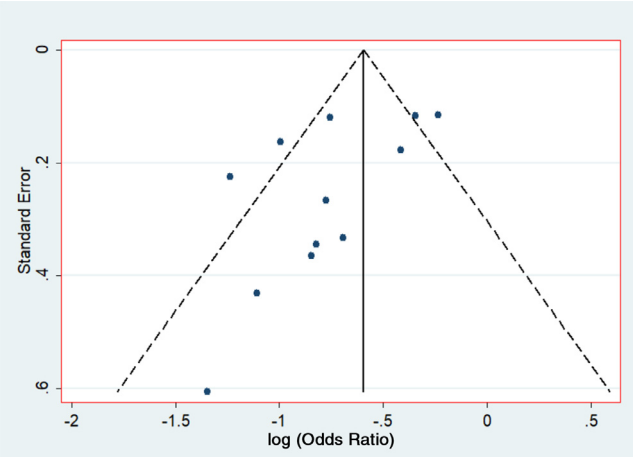

Figure 2. Funnel plot for risk of relapse with 95% confidence limits.

excluded because they did not have an eligible study population, had no proper control group, or did not directly measure the association between cGVHD and PDR. Finally, we included 11 studies, which were all retrospective observational studies, comprising a total of 64,239 participants. The median age range was 9–51 years, and the median follow-up duration ranged from 24 to 96 months.

Meta-analysis results

Eleven studies were included in this meta-analysis. Using a random-effects model, we found a significant decrease in the risk of PDR in the cGVHD group, compared with the control group (no-cGVHD group), with the pooled risk ratio being 0.49 (95% confidence interval [CI]: 0.40–0.61, $I^2 = 69.3\%$) (Figure 3). There were no significant changes in pooled risk ratios after we conducted sensitivity analysis by removing each study from the pooled cohorts.

The funnel plot revealed publication bias, which was not statistically significant according to Egger's test ($p = 0.066$). This was likely due to the lower likelihood of negative studies being selected for publication.

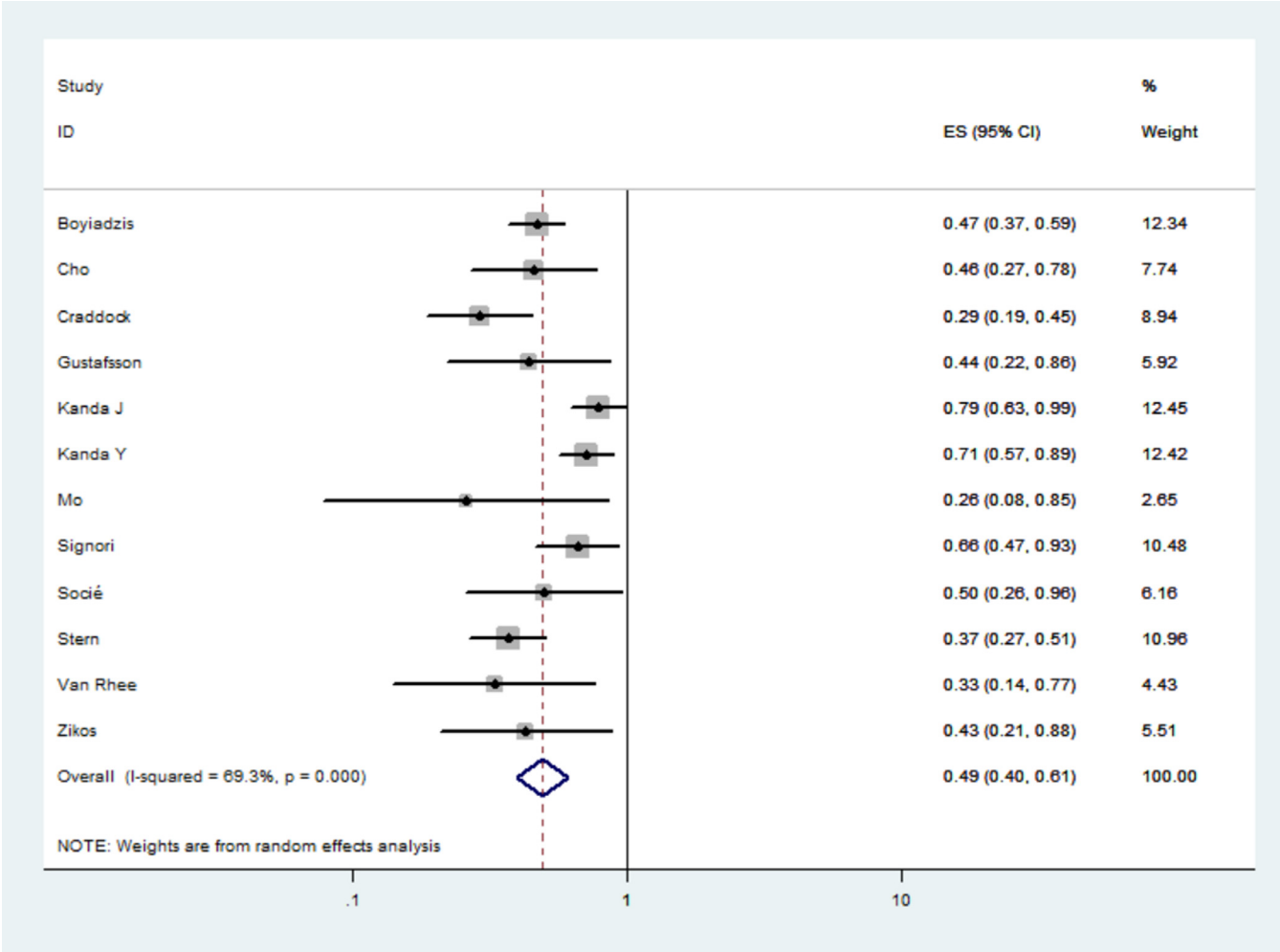

Figure 3. Main meta-analysis result.

Table 1. Study characteristics

Trial name	Country	Publication year	Study design	Population	Median age	% Male	Conditioning regimen (%)	Transplant indication	Graft source	GVHD diagnosis	GVHD ppx (%)	ATG (%)	Alem (%)	HLA matching (%)	Average follow up time (mo)	NOS score
Boyiadzis et al. [9]	CIBMTR registry	2015	ROS	7,489	36	57	MAC 100	AML, ALL, CML, MDS	BM 72% PB 28%	CIBMTR criteria	CsA 77 CNI 13 Other 10	14	N/A	MRD 52 MUD 19 PMUD 18 MMUD 11	93	9
Cho et al. [17]	Korea	2012	ROS	775	36	55	MAC 70 RIC 30	AML, CML, MDS, ALL, PCD	BM 62% PB 38%	NIH criteria 2005	CNI 100	N/A	N/A	MRD 63 MUD 20 PMUD 13 MMUD 4	41	9
Craddock et al. [10]	EBMT	2018	ROS	2028	51	51	MAC 51 RIC 49	AML in CR1	BM21% PB79%	N/A	N/A	93	7	MRD 44 MUD 56	36	7
Gustafsson Jernberg et al. [11]	Sweden	2003	ROS	169	9	63	MAC 100	ALL, AML	BM 92 PB 8%	N/A	CsA 73 Other 27	29	N/A	MRD 63 MUD 19 MMRD 9 MMUD 9	84	8
Kanda et al. [18]	Japan	2017	ROS	2558	50	56	MAC 65 RIC 35	AL, MDS	UC 100%	NIH criteria 2005	CsA/CNI based 100	N/A	N/A	MUD 6 PMUD 94	35	9
Kanda et al. [15]	Japan	2004	ROS	1514	35	61	MAC 100	AML, ALL CML, MDS	BM 100%	Seattle criteria	CsA/MTX 100%	N/A	N/A	MRD 100	N/A	9
Mo et al. [12]	China	2015	ROS	101	26	55	MAC 100	AL, MDS	BM + PB 100%	NIH criteria 2005	CsA 80 MTX 21	43	N/A	MRD 43 PMRD 57	24	9
Signori et al. [13]	Italy	2012	ROS	802	41	56	MAC 67 RIC 33	AML, ALL, CML, CLL, PCD, HL, NHL	BM 57% PB 43%	Seattle criteria	CsA/MTX 100	68	N/A	MUD 100	25	9
Socié et al. [14]	Germany	2011	ROS	201	40	53	MAC 100	AML, CML, ALL, MDS, OMF	BM18% PB 82%	Seattle criteria	CsA/MTX 100	51	N/A	MUD 17 MMUD 83	36	8
Stern et al. [16]	EBMT	2014	ROS	48,111	44	58	MAC 60 RIC 33%	AML, ALL, CML, CLL, PCD, HL, NHL	BM27 PB71%, UC 2%	Seattle criteria	N/A	N/A	N/A	MRD 58 MUD 30 MMUD 12	N/A	9
Van Rhee et al. [19]	EBMT	1997	ROS	373	31	56	MAC 100%	CML	BM 100%	Seattle criteria	CsA based 100	N/A	N/A	MRD 100	96	9
Zikos et al. [20]	Italy	1998	ROS	118	22	63	MAC 100%	ALL	BM83% PB 17%	Seattle criteria	CsA/MTX 80 MTX 7	N/A	13	MRD 87 MMRD 11 MUD 2	72	9

CIBMTR registry=Center for International Blood and Marrow Transplant Research; EBMT=European Group for Blood and Marrow Transplantation; ROS=retrospective observational study; MAC=myeloablative; RIC=reduced intensity conditioning; AML=acute myeloid leukemia; CML=chronic myeloid leukemia; ALL=acute lymphoid leukemia; CLL=chronic lymphoid leukemia; MDS=myelodysplastic syndrome; PCD=plasma cell disorder; HL=Hodgkin's lymphoma; NHL=non-Hodgkin's lymphoma; OMF=osteomyelofibrosis; BM=bone marrow stem cell; PB=peripheral blood stem cell; UC=umbilical cord blood stem cell; CsA=cyclosporine; CNI=calcinurin inhibitor; MTX=methotrexate; ATG=anti-thymocyte immunoglobulin; Alem=alemtuzumab; MRD=match-related donor; MUD=match unrelated donor; PMUD=partially match-unrelated donor; MMRD=mismatch-related donor; MMUD=mismatch-unrelated donor; MD=match donor; PMD=partially match donor; NOS=Newcastle-Ottawa Quality Assessment Scale.

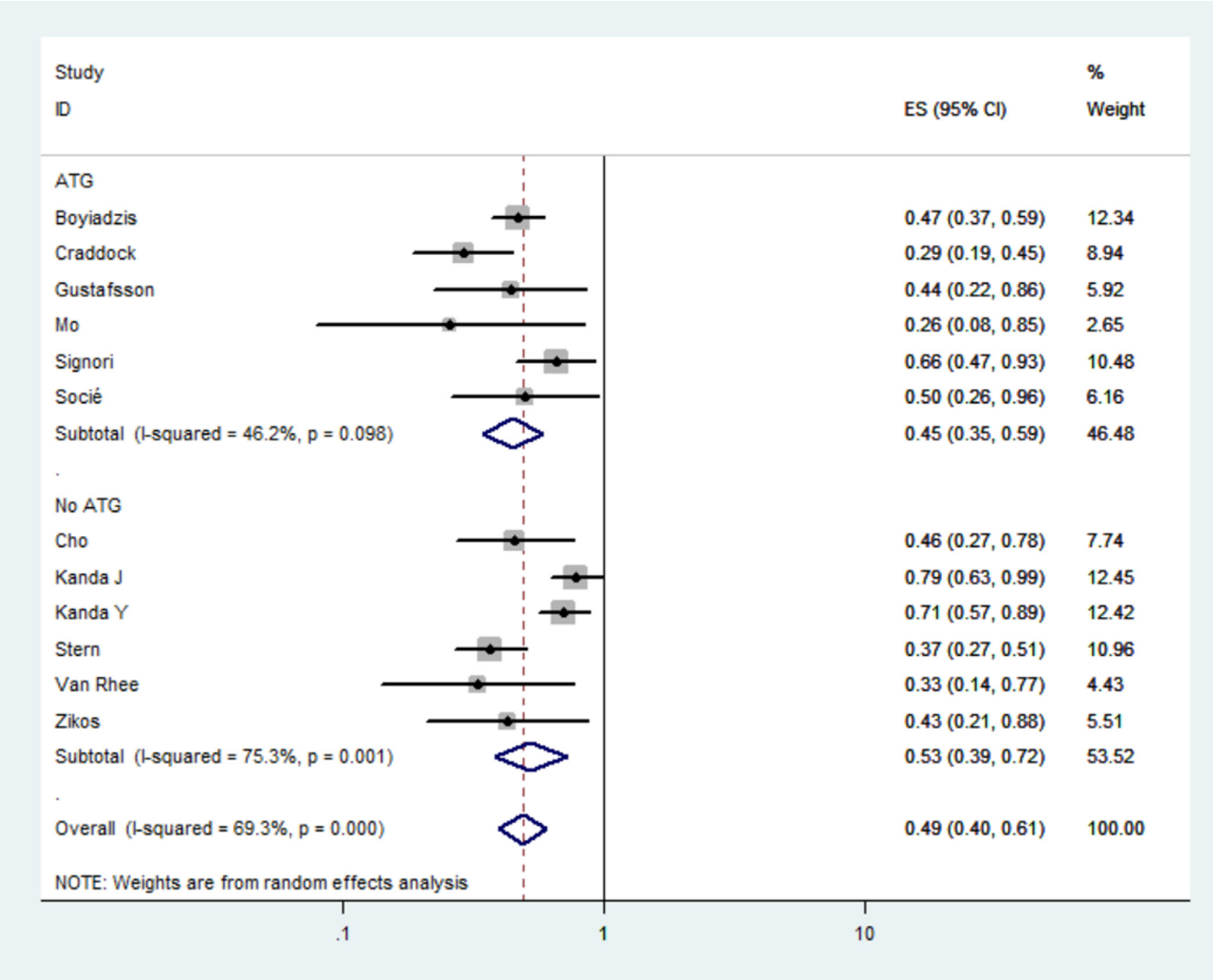

Figure 4. Main meta-analysis result: 11 studies included in this meta-analysis. Using a random-effects model; we found a significant decrease in the risk of PDR in the cGVHD group, compared to the control group with the pooled risk ratios of 0.49, 95% CI 0.40-0.61, I2=69.3%.

Subgroup analysis

We conducted a subgroup analysis to assess the effect of ATG use and degree of HLA mismatch on the primary outcome.

First, for the use of ATG, we categorized the studies into one group in which ATG was part of the in vivo T-cell depletion process [9–14] and another group in which ATG was not used [15–20]. The pooled risk ratio for the ATG group was 0.45 (95% CI: 0.35–0.59, $I^2 = 46.2\%$), and the pooled risk ratio for the group that did not use ATG was 0.53 (95% CI: 0.39–0.72, $I^2 = 75.3\%$) (Figure 4).

Second, when we categorized the studies based on the HLA matching process, the first group used only stem cells with well matched or partially matched HLA [10–13,15,18,19]. The other group included HLA-mismatched grafts [9,14,16,17,20]. We found that the group that utilized mismatched stem grafts had a pooled risk ratio of 0.44 (95% CI: 0.37–0.52, $I^2 = 0\%$), and the group that did not use HLA-mismatched grafts had a pooled risk ratio of 0.53 (95% CI: 0.39–0.71, $I^2 = 73\%$) (Figure 5).

For graft source, we divided the graft sources into peripheral blood (PB), bone marrow (BM), and umbilical cord (UC). We found that the study that used both PB and BM [10–14,17,20] had a risk ratio (RR) of 0.46 (95% CI: 0.38–0.56, $I^2 = 25.1\%$). For the group that used only BM [15,19], the RR was 0.54 (95% CI: 0.26–1.11, $I^2 = 66\%$), and for the group that included UC [16,18], the RR was 0.55 (95% CI: 0.26–1.15, $I^2 = 93.1\%$) (Figure 6).

And lastly, for the GVHD prophylaxis regimen, we divided the regimen into cyclosporine A-based (CsA), calcineurin inhibitor-based (CNI), methotrexate-based

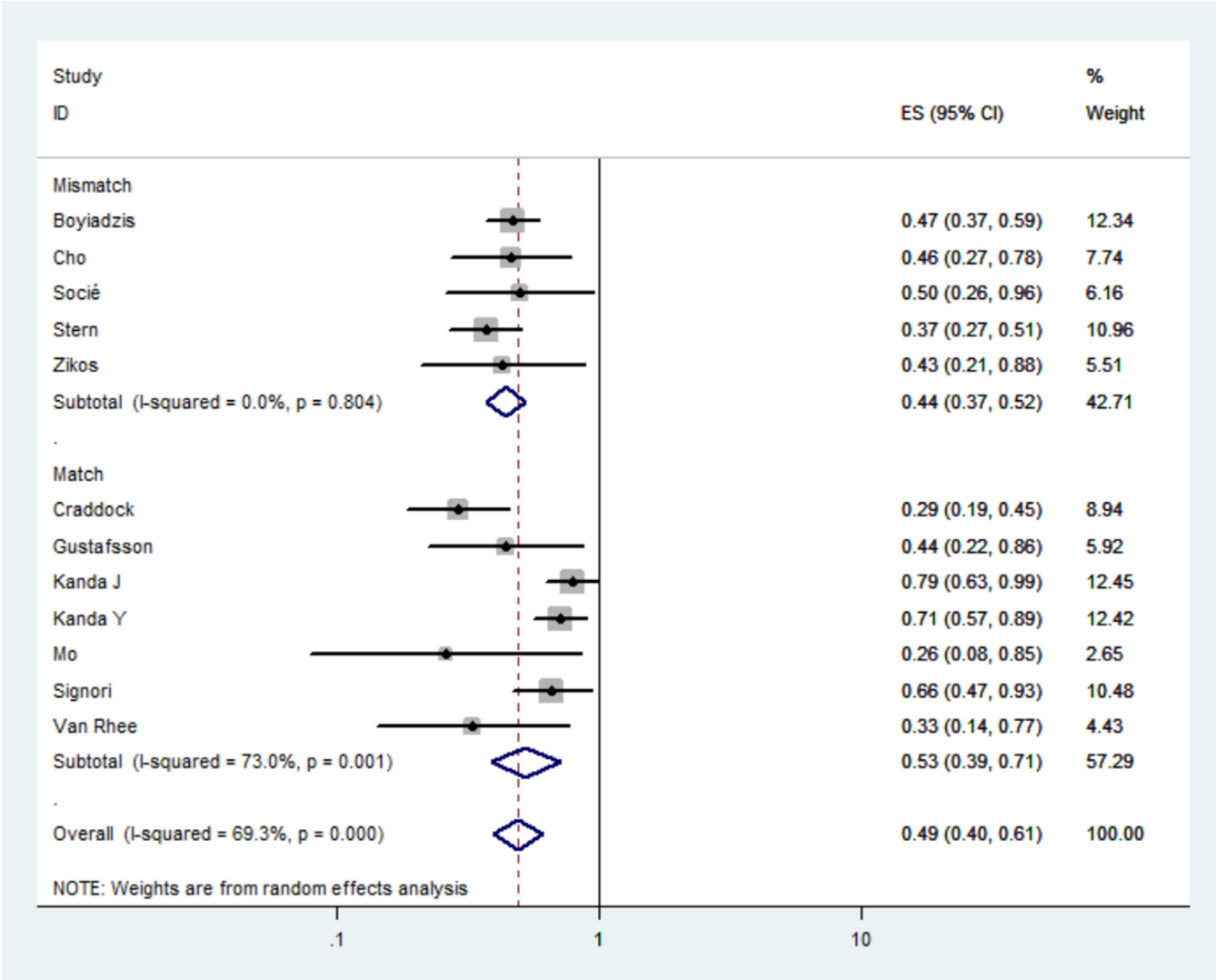

Figure 5. Subgroup analysis based on ATG use: Studies that used ATG had pooled risk ratio of 0.45, 95% CI 0.35-0.59, I2=46.2% and the group that did not use ATG had pooled risk ratio of 0.53, 95% CI 0.39-0.72, I2=75.3%.

(MTX), and other regimens. We found that the group that used CsA-based regimens [9,11,12,15,19] had an RR of 0.5 (95% CI: 0.36−0.68, $I^2 = 59.5\%$). For the group that used CNI-based regimens [17], the RR was 0.46 (95% CI: 0.27−0.78, $I^2 = 0\%$). For the group that used both CsA and CNI in their regimens [18], the RR was 0.79 (95% CI: 0.63−0.99, $I^2 = 0\%$). For group that used CsA- and MTX-based regimens [13,14,20], the RR was 0.59 (95% CI: 0.44−0.78, $I^2 = 0\%$), and for the group that used other regimens [10,16], the RR was 0.34 (95% CI: 0.26−0.44, $I^2 = 0\%$) (Figure 7).

According to this regression meta-analysis, use of ATG in the transplant protocol and use of HLA-mismatched grafts had the potential to modify the association between cGVHD and PDR, which could be used to identify the high-risk population. Therefore, we concluded that cGVHD is significantly associated with PDR. This observed association was stronger among studies that used HLA-mismatched grafts and ATG.

Discussion

There has long been speculation that the presence of cGVHD signifies persistent active T-cell function against the host antigen, which is viewed as a surrogate marker for continued suppression of host malignant cells and, therefore, prevents PDR. There are multiple theories behind this mechanism including "T-cell alloreactivity," as explained by Bhushan et al. [21], which involved mediators from cytotoxic as well as effector T cells in a manner similar to an autoimmune phenomenon [22,23].

These findings signify that the GVT effect plays a vital role in preventing PDR, causing potent "adoptive cellular immunotherapy" [24]. Horowitz et al. [25] also

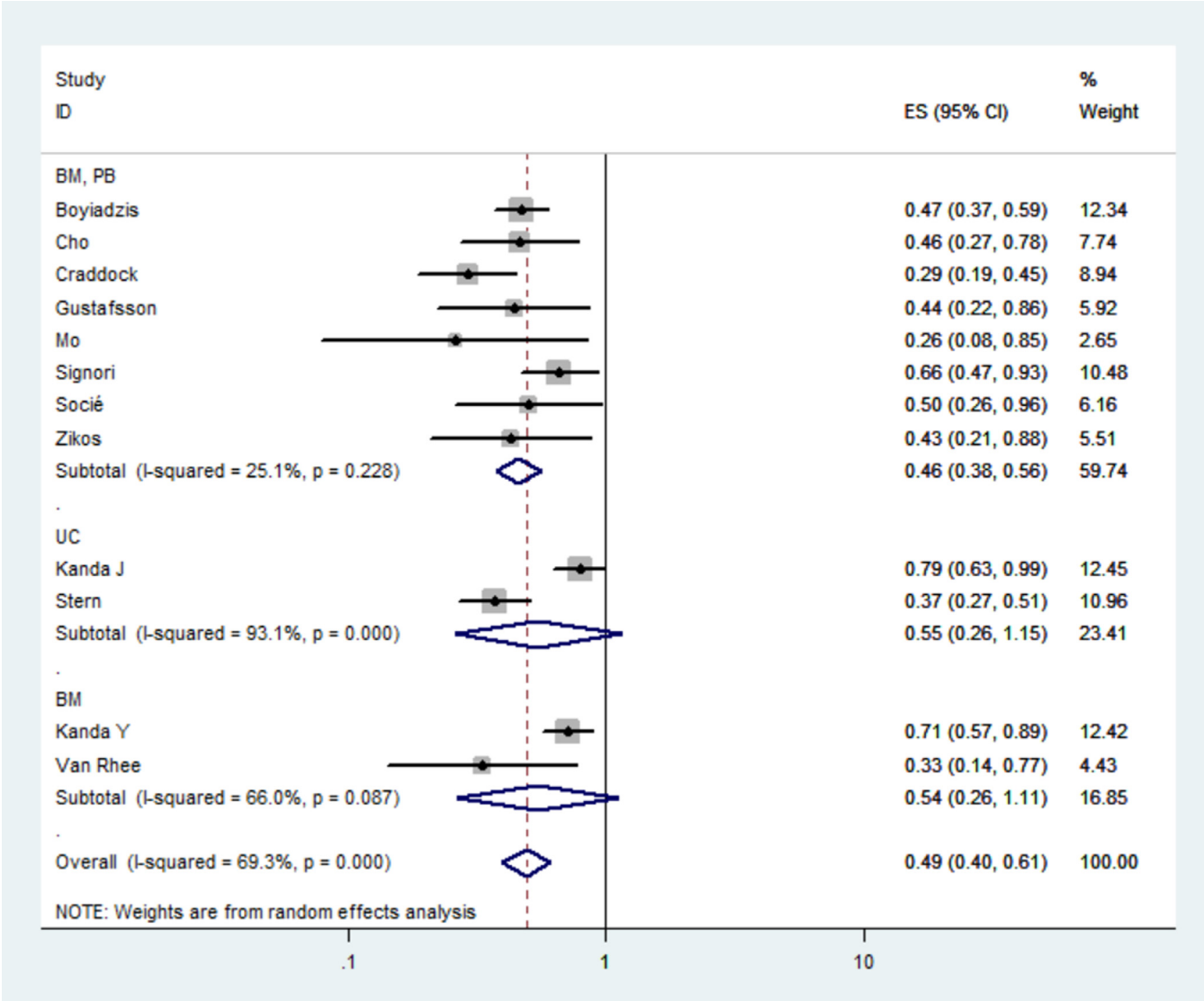

Figure 6. Subgroup analysis based on HLA matching Studies that only include well matched graft had pooled risk ratio of 0.53, 95% CI 0.39-0.71, I2=73% while the studies that include mismatch graft had pooled risk ratio of 0.44, 95% CI 0.37-0.52, I2=0%.

proposed that because of the aforementioned mechanism, the magnitude of the GVT effect significantly correlates with the severity of GVHD, meaning that the relapse rate was lowest in patients with severely extensive cGVHD as compared with other types of GVHD.

Other evidence supporting this proposed mechanism is the effect of the myriad ways of manipulating T-cell function. For example, donor lymphocyte infusion (DLI) can be used to salvage patients in the relapse state as it enhances the GVT effect, similar to a second allogenic transplantation [26–29].

As traditional chemotherapy alone cannot completely eliminate all malignant cells from the primary disease, successful engraftment is needed to continue the cytotoxic reaction of the donor T cells that can target and destroy any residual malignant cells. It is fair to conclude that low-grade cGVHD is probably the most desirable outcome for patients undergoing HSCT for malignant hematologic conditions [9].

We found more consistent outcomes in our subgroup analysis of patients transplanted with some degree of HLA mismatch and the use of protocols containing ATG. This result could be related to the fact that the degree of HLA mismatch correlates with the severity of GVHD and GVT, thus conferring a lower relapse rate [30]. The other modifying factor is the incorporation of ATG into the transplant protocol, which significantly decreases the risk of both GVHD and relapse, suggesting that ATG can enhance the GVT effect without increasing the risk of GVHD [31–33].

There are some limitations to this study. First, we included only 11 studies related to hematologic malignancies. This could limit the external generalizability

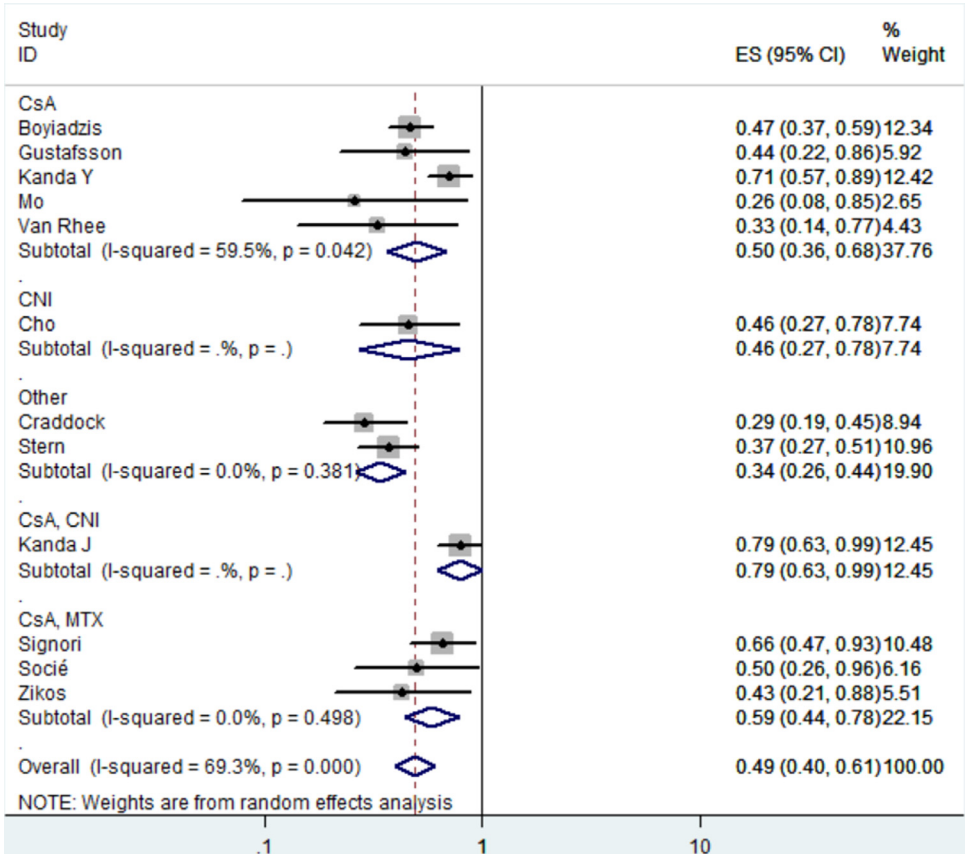

Figure 7. Subgroup analysis based on graft type Studies that used both BM and PB had pooled risk ratio of 0.46, 95% CI 0.38-0.56, I2=25.1% while the group that used only BM graft had pooled risk ratio of 0.54, 95% CI 0.26-1.11, I2=66% and the group that only used UC had pooled risk ratio of 0.55, 95% CI 0.26-1.15, I2=93.1%.

of this meta-analysis beyond other diseases. Second, we included studies with patients of all ages with various indications for transplant, patients with several pre-transplant co-morbidities, and patients with various disease statuses. These differences could account for the heterogeneity of our outcome. Moreover, we realized that once diagnosed with cGVHD; the patients would require more frequent follow-up, therefore increasing the possibility of detecting the early phase of relapse.

Lastly, we recognized that patients with cGVHD suffer devastating long-term side effects. This includes the involvement of several organs such as the skin, gastrointestinal tract, liver, and, less frequently, the liver and eyes [9]. Different degrees of cGVHD also determine the impact on quality of life of HSCT survivors. Also, with the need for long-term suppressant use, infection is a common side effect. as are frequent hospital visits [34–36]. Despite all this, according to our study, the presence of cGVHD could potentially benefit the patient's overall improved prognosis in terms of decreasing the risk of PDR. Research regarding cGVHD on the molecular and cellular levels is ongoing, to potentiate the GVT effect but minimize the process of cGVHD at the same time.

Our meta-analysis of observational studies revealed that cGVHD is statistically associated with PDR. However, there is insufficient evidence to conclude that this association is causal as all included studies are observational studies. Thus, there is a need for further research to optimize transplant protocols and circumvent these complications. We suggest that large, prospective, controlled trials are warranted to investigate the more delicate details of the proposed association between cGVHD and PDR.

Conflict of interest disclosure

The authors declare that they have no conflict of interest.

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