Engraftment Syndrome and Acute Graft-versus-Host Disease: A Meta-Analysis

Kittika Poonsombudlert MD; Jakrin Kewcharoen MD; Chattip Prueksapraopong MD; and Nath Limpruttidham MD

Abstract

Engraftment syndrome (ES) has been associated with the surge of neutrophils and cytokines, which is similar to the presumed underlying pathophysiology behind acute graft-versus-host disease (aGVHD). However, there has been no meta-analysis to evaluate the association; therefore, the team attempted to verify an association between ES and aGVHD through meta-analysis. The team searched for titles of articles in MEDLINE (PubMed), the Cochrane Library, and the EMBASE database up until December 2018 that evaluated the association between ES and aGVHD and conducted a random effect meta-analysis of 8 studies involving a total of 1,945 participants to report the pooled odds ratio (OR) for association of ES and aGVHD. The team found a significantly increased odds of developing aGVHD in patients with ES with the pooled OR of 2.76 (95% confidence interval [CI]: 1.64-4.63) and an $I^2 = 64.5\%$. In conclusion, patients with ES have significantly higher odds of developing aGVHD compared to patients without ES.

Keywords

engraftment syndrome, auto-aggression syndrome, capillary leakage syndrome, acute graft-versus-host disease, meta-analysis

Abbreviations

aGVHD = Acute graft-versus-host disease
CI = Confidence interval
CsA = Cyclosporine A
ES = Engraftment syndrome
HLA = Human leukocyte antigen
HSCT = Allogenic hematopoietic stem cell transplant
NOS = Newcastle−Ottawa Quality Assessment Scale
OR = Odds ratio
PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses
UC = Umbilical cord stem cells

Introduction

Allogenic hematopoietic stem cell transplant (HSCT) has remained a common treatment for many malignant hematologic conditions, despite being riddled with various complications. During the process of HSCT, patients are infused with stem cells from the donor, and only when the stem cells home to the patient's bone marrow and start to produce normal blood cells, patients are then labeled as "engrafted." One discovery in 1997 found that some patients who were in the engrafting process developed a constellation of findings, including non-infectious fever and skin rash, as well as other inflammatory phenomena. This constellation of symptoms was originally termed "auto-aggression syndrome",[1,2] but is now called engraftment syndrome (ES), which occurs near the start of the myeloid recovery. As ES is closely related to the return of the neutrophils, it has been linked with cytokine storm in multiple levels of pro-inflammatory mediators secreted by the neutrophils, and later, the term "capillary leakage syndrome" was used.[3-5] Because of its resemblance to the findings of acute graft-versus-host disease (aGVHD) in both clinical and diagnostic features, ES and aGVHD have been closely associated and initially were thought of as the same entity or an overlap syndrome.[6] It is challenging to distinguish ES and early aGVHD by a non-expert hematologist even today.[7,8]

Two of the most widely used criteria for ES diagnosis were developed by Maiolino, et al, and Spitzer, et al, in 2003 and 2001, respectively.[9,10] However, since the Spitzer criteria are more refined and explicit, it has been more widely adopted. Both criteria are compared in Table 1.

Table 1. Comparison Between Spitzer and Maiolino Criteria for Engraftment Syndrome Diagnosis

	Spitzer Criteria[a]	Maiolino Criteria[b,c]
Major criteria	1. Non-infectious fever, body temperature ≥ 38.3°C 2. Erythematous skin rash involving > 25% of body surface area; excluding drug allergy 3. Non-cardiogenic pulmonary edema and hypoxia	Non-infectious fever
Minor criteria	1. Hepatic dysfunction (either bilirubin≥ 2 mg/dL or transaminase levels ≥ 2 times normal) 2. Renal insufficiency (serum creatinine ≥ 2 times baseline) 3. Weight gain ≥ 2.5% of baseline body weight 4. Transient encephalopathy unexplainable by other causes.	1. Skin rash 2. Pulmonary infiltrates 3. Diarrhea
Timing to myeloid recovery	Within 4 days of absolute neutrophil count > 500	Within 24 hours of the presence of neutrophil

[a] Vriesendorp HM, Heidt PJ, et al. History of Graft-Versus-Host Disease. *Exp Hematol.* 2016;44:674-88. doi: 10.1016/j.exphem.2016.05.011.
[b] Roddy JV, Haverkos BM, McBride A, et al. Tocilizumab for Steroid Refractory Acute Graft-Versus-Host Disease. *Leuk Lymphoma.* 2016;57:81-5. doi: 10.3109/10428194.2015.1045896.
[c] Dignan FL, Clark A, Amrolia P,et al. Haematology Haemato-oncology Task Force of British Committee for Standards in, Blood British Society for, and Transplantation Marrow, Diagnosis and Management of Acute Graft-Versus-Host Disease. *Br J Haematol.* 2012;158:30-45. doi: 10.1111/j.1365-2141.2012.09129.x

As more HSCT are being performed, close monitoring, and advanced diagnostic tests have been able to identify more cases of ES and aGVHD. There have been retrospective analyses that suggest a close correlation between ES and aGVHD, but no detailed analysis between different stem cell sources and aGVHD prophylaxis regimen has not been explored; therefore, the team decided to evaluate the correlation between ES and aGVHD through meta-analysis.

Methods

The team performed a systematic review of the literature according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[11] The team searched for titles of articles in MEDLINE (PubMed), the EMBASE database, and the Cochrane Library up until December 2018. The following medical search terms were used: engraftment syndrome, auto-aggression syndrome, capillary leakage syndrome, and acute graft-versus-host disease (Figure 1).

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

The study included patients with all disease statuses as well as all methods of conditioning regimens. There was no restriction based on the patient's age, indication for transplant, data sources, or the study location. Due to the unavailability of details regarding the degree of Human Leukocyte Antigen (HLA) and gender matching, these data were also not restricted. Studies done in cellular or animal models were not included.

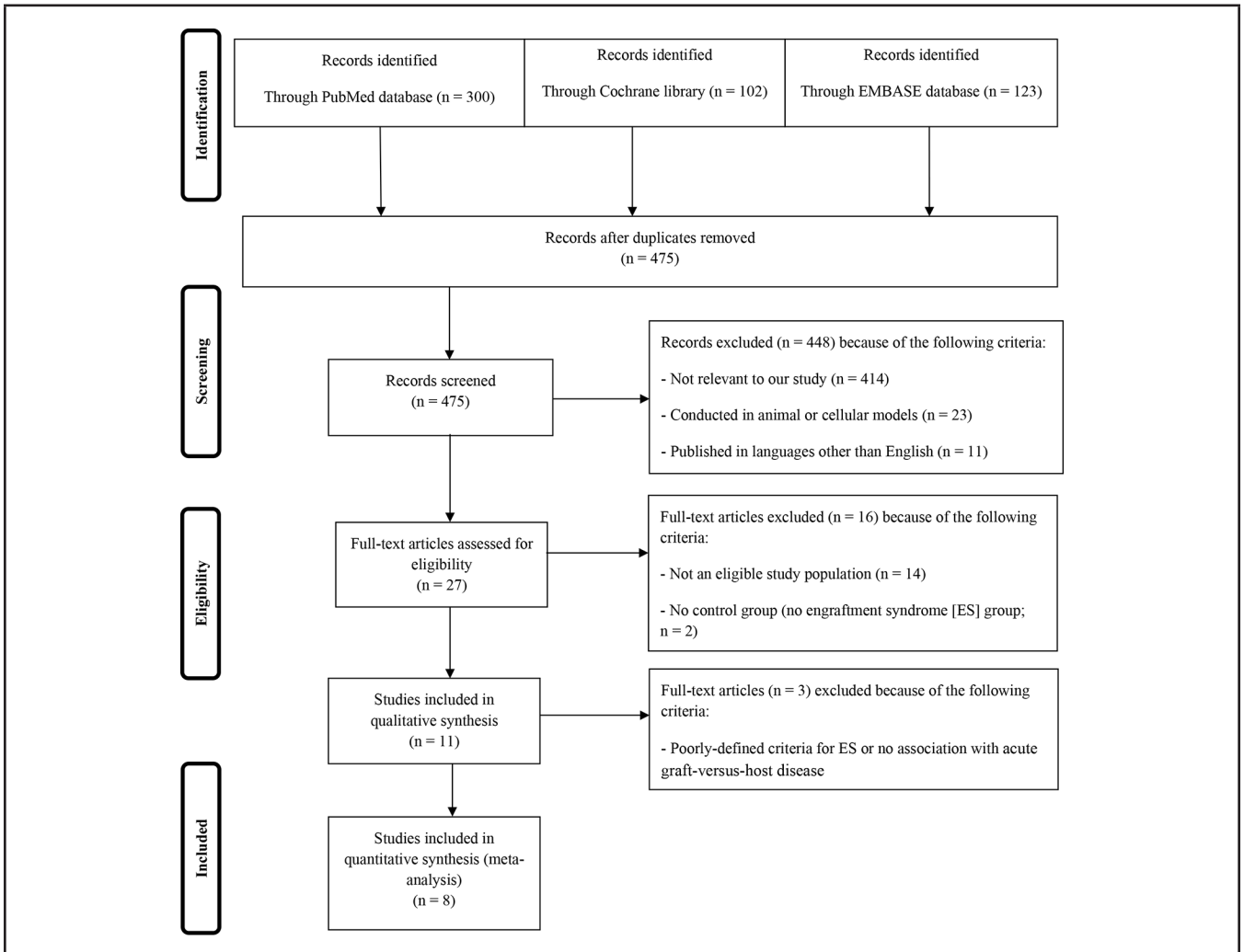

Figure 1. Summary of Search Strategy: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram Demonstrating the Search Strategy Including Study Identification, Study Screening, Eligibility of the Study and Inclusion of the Study

Data Extraction and Quality Assessment

Two investigators independently extracted the following data from each article: 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 the selection of the study groups, comparability of study groups, and ascertainment of exposure/outcome.[12] Studies with total scores of > 6 and < 4 were considered to be of high and low quality, respectively. The team excluded any studies that scored < 4. There were no blinded control trials included in our study.

Statistical Methods

The primary outcome was the odds of developing aGVHD among patients with ES versus the control group (no ES group). The team used a random-effects model as all the included studies were retrospective observational studies to determine the pooled odds ratio (OR) and 95% confidence interval (CI) for the outcome. The team conducted sensitivity analysis and subgroup analysis to explore heterogeneity of the included studies using the I^2 statistic.[13] The team also performed Funnel plot and Egger's test to assess for publication bias. All analyses were performed using Stata 13 software (StataCorp LLC, College Station, TX) at $P < .05$ level of significance.

Results

Description of Included Studies

The initial search yielded 475 articles. Of these articles, 448 were excluded from the title and abstract review because they were not relevant to our study (n = 414), conducted in animal or cellular models (n = 23), or published in languages other than English (n = 11). A total of 27 articles underwent full-length review; 16 of them were excluded because they did not have an eligible study population (n = 14) or had no proper control group (no ES group; n = 2), and 3 studies did not directly measure the risk of aGVHD and ES. The final analysis included 8 unique studies, which were all retrospective case-control studies, and used the Spitzer criteria for the diagnosis of engraftment syndrome. resulting in a total of 1945 patients. Of these patients, 397 who had ES were defined as the case group, and 1548 patients who did not have ES were defined as the control group. A summary of the search strategy is illustrated in Figure 1.

Table 2 describes the characteristics of the extracted studies. The sample size of the studies varied from 52 to 927 patients, with median age of each study ranging from 7 to 53 years. The average follow-up duration was from 9 to 114 months.

Meta-Analysis Results

There were 8 studies included in this meta-analysis. Using a random-effects model, the team found a significant increase in the odds of aGVHD in ES group versus the control group with the pooled OR of 2.76 (95% CI: 1.64-4.63) and an $I^2 = 64.5\%$ (Figure 2).

The team did not find publication bias from Funnel plot (Figure 3) and Egger's test (Figure 4) was not statistically significant ($P = .573$).

Subgroup Analysis

The team conducted a subgroup analysis to assess the effect of source of hematopoietic stem cell and aGVHD prophylaxis regimen on the primary outcome.

First, for the source of hematopoietic stem cell, the team categorized the studies that used only umbilical cord blood (UC) as stem cell source,[13-16] and the studies that used other types of stem cells as another group.[17-20] As shown in Figure 5, the pooled OR among the UC group was 3.93 (95% CI: 2.07-7.55, $I^2 = 57.1\%$), and for the other types of stem cells (mix group), the pooled OR was 1.83 (95% CI: 1.22-2.77, $I^2 = 0\%$).

In addition, when the team categorized the aGVHD prophylaxis regimen into Cyclosporine (CsA)-based group,[15,16,18-20] and another group that uses other types of aGVHD prophylaxis regimen,[13,14,21] the pooled OR for the CsA group was 2.62 (95% CI: 0.97-7.05, $I^2 = 85.2\%$), and for the group with other types of aGVHD prophylaxis regimen, the pooled OR was 2.78 (95% CI: 1.53-5.05, $I^2 = 34\%$; Figure 6).

Table 2. Summary of the Characteristics of 8 studies Included in the Meta-Analysis on the Association Between Engraftment Syndrome (ES) and Acute Graft-Versus-Host Disease (aGVHD)

Study name	Country	Publication Year	Population (ES/ no ES)	Median age (year)	% male	Transplant indication	Stem cell source	Conditioning regimen	Average time to ES diagnosis (days)	aGVHD prophylaxis	Steroid treatment	Average Follow-up time (months)
Chang	US	2014	927 (119/808)	51	60	HC	PB, BM, UC	MAC 63.1% RIC 36.9%	10	Tac+MTX 59.6%, Tac+MMF 37.9%	mPSL 94/119	49
Ileri	Turkey	2016	169 (17/152)	11.3	56.8	HC	PB, BM	MAC 82% NMAC 18%	13	CsA40.8% CsA+MTX 59.2%	mPSL 13/17	64
Kanda	US	2013	57 (15/42)	28	49	MHC	UC	MAC 100%	12	Tac+MMF 61%, CsA+MMF 39%	SS 24/44	22
Omer	US	2014	217 (48/169)	53	58	HC	PB, BM, UC	MAC 38.7% NMAC 61.3%	14	CsA 39.6%, CsA+MTX 13.8%, CsA+MMF 15.7%	mPSL 34/48	21
Park	Korea	2013	381 (102/279)	7.2	58	HC	UC	MAC 68.5% RIC 31.5%	7	MTX and/or STR NOS	SS 74/102	74
Patel	US	2010	52 (16/36)	38	54	MHC	UC	MAC 69.2% NMAC 30.8%	9	CsA+MMF NOS	mPSL 16/16	12
Schmid	Germany	2008	61 (29/32)	7.8	54	HC	PB, BM	MAC 100%	16	CsA+MTX 100%	PSL 8/29	114
Wang	China	2011	81 (51/30)	18	69	MHC	UC	MAC 89% RIC 11%	7	CsA+MMF 100%	mPSL 47/51	9

Abbreviations
ES; engraftment syndrome, no ES; no engraftment syndrome (control group)
Transplant indication: HC; hematologic conditions, MHC; malignant hematologic conditions
Stem cell source: UC; umbilical cord blood stem cell, PB; peripheral blood stem cell, BM; bone marrow stem cell
Conditioning regimen: MAC; myeloablative, NMAC; non- myeloablative, RIC; reduced intensity conditioning regimen
aGVHD prophylaxis: MMF; Mycophenolate mofetil, CsA; Cyclosporine A, Tac: Tacrolimus, MTX; Methotrexate, STR; steroid, NOS; not otherwise specified
Steroid treatment: SS; intravenous systemic steroid unspecified, mPSL; intravenous Methylprednisolone, PSL; Prednisolone

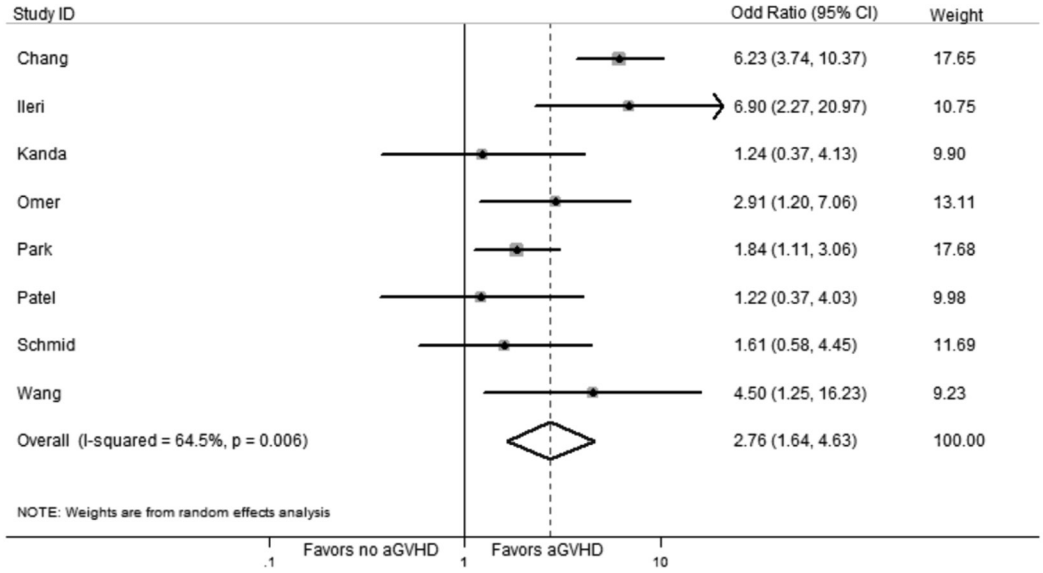

Figure 2. Forest Plot Demonstrating Association of Engraftment Syndrome and Acute Graft-Versus-Host Disease (aGVHD). [Horizontal line represents 95% confidence interval CI.]

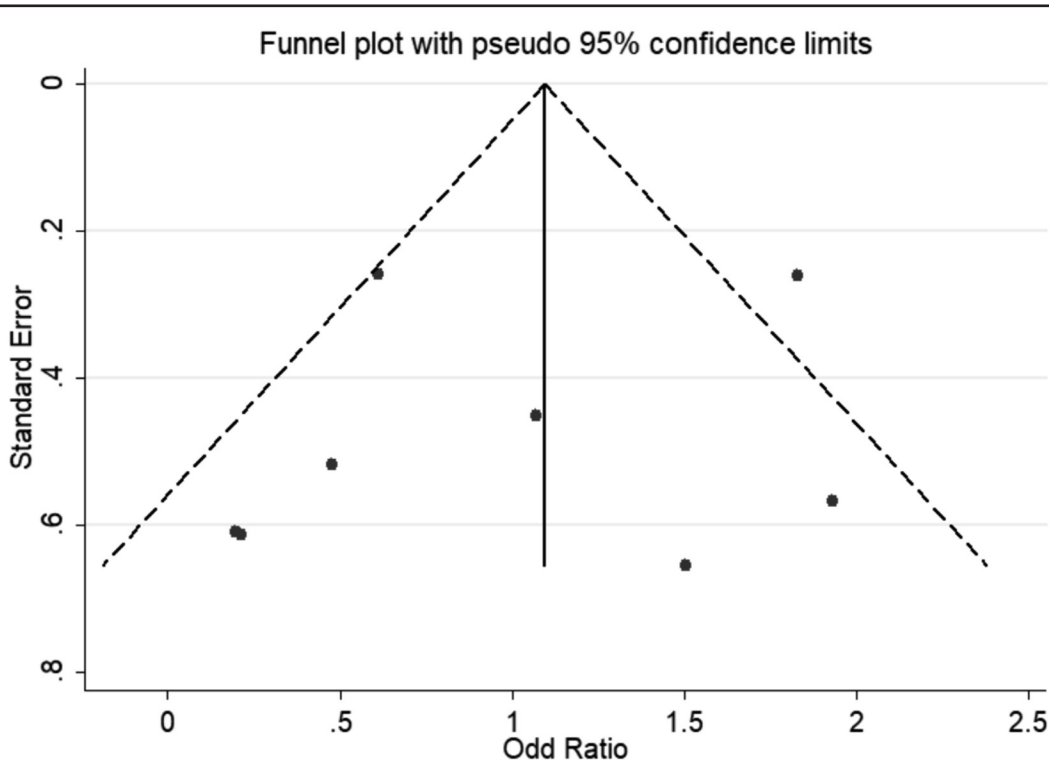

Figure 3. Funnel Plot of Acute Graft-Versus-Host Disease and Engraftment Syndrome. [Circles represent published studies.]

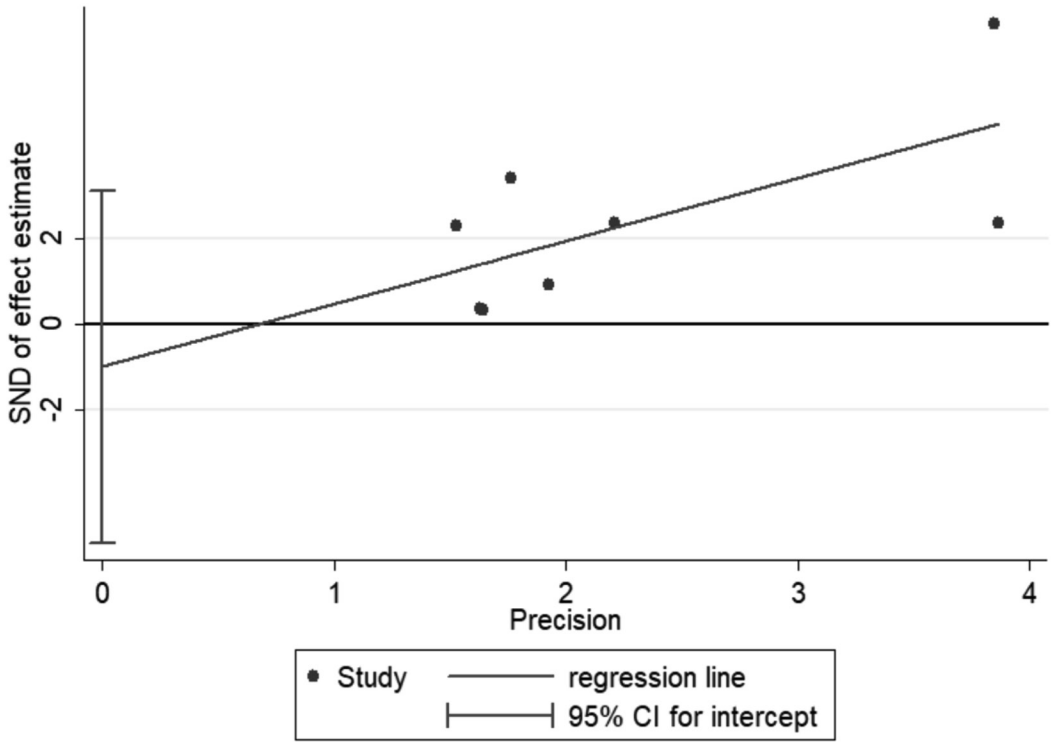

Figure 4. Graph of Egger's Test for Publication Bias in the Studies of the Meta-Analysis. Vertical Axis Represents Standard (SND) of Effect Estimate of the Odd of Acute Graft-Versus-Host Disease in Engraftment Syndrome Patients Compared with Controls. [Vertical line represents 95% confidence interval (CI).]

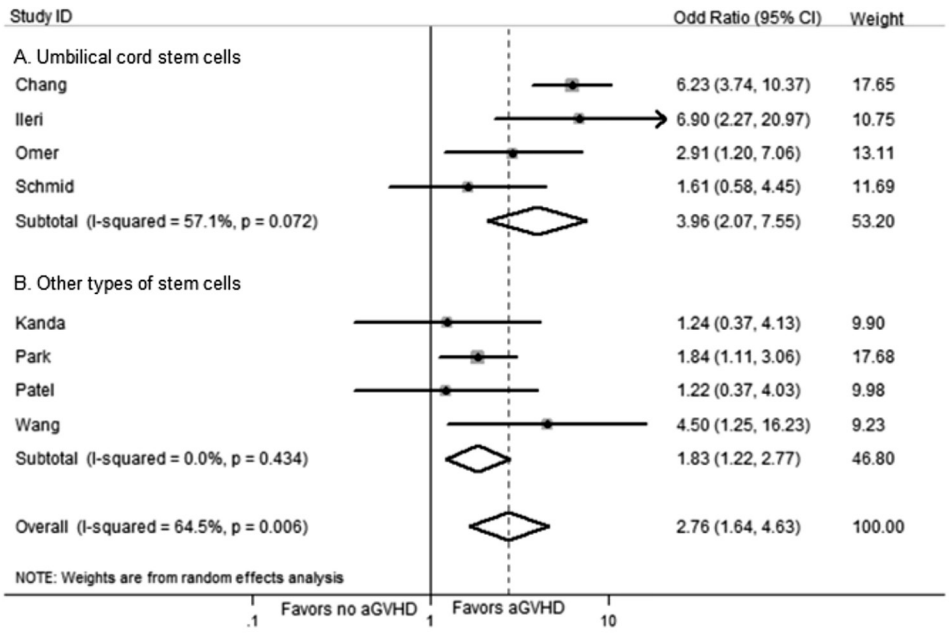

Figure 5. Forest Plot Demonstrating Association of Engraftment Syndrome and Acute Graft-Versus-Host Disease (aGVHD) by Stem Cell Source. A. Umbilical Cord Blood Stem Cell. B. Non-Umbilical Cord Blood. [Horizontal line represents 95% confidence interval (CI).]

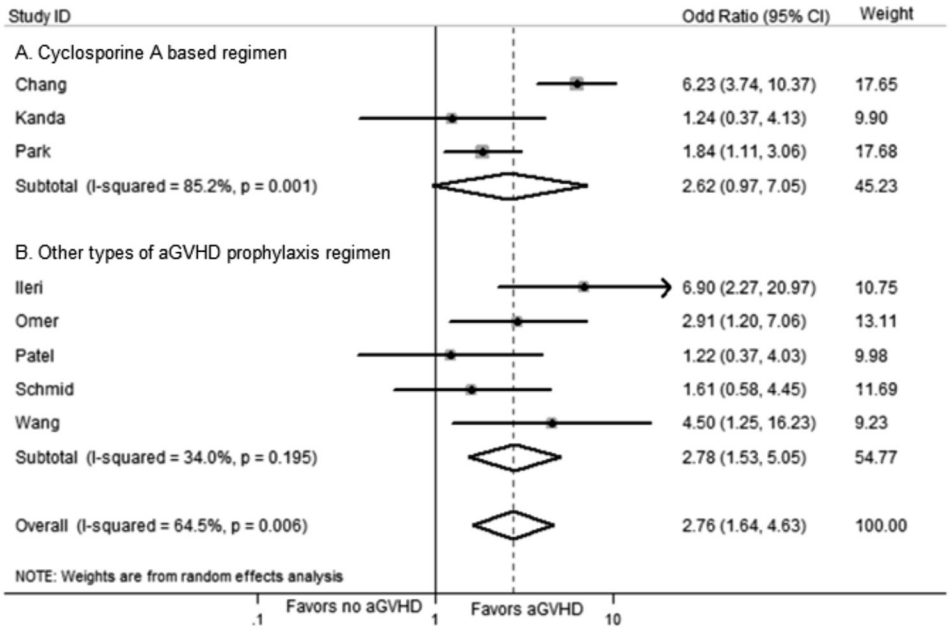

Figure 6. Forest Plot Demonstrating Association of Engraftment Syndrome and Acute Graft-Versus-Host Disease (aGVHD) by aGVHD Prophylaxis Regimen. A. Cyclosporine A-Based Regimen. B. Non-Cyclosporine A-Based Regimen. [Horizontal line represents 95% confidence interval (CI).]

Discussion

There have been retrospective analyses that suggest a close correlation between ES and aGVHD. To the best of the researchers' knowledge, this study is the first to evaluate the association between the 2 entities by means of meta-analysis. Past studies suggested that ES and aGVHD have similar clinical features and underlying pathophysiology, but no strong positive correlation has been confirmed and therefore further research was recommended to further explore the causality between ES and aGVHD.

There have been many theories trying to explain the pathophysiology of ES. The initial theory believed ES to be mediated by mediators from the T cells and other innate immune responses triggered by a foreign antigen from the newly engrafted in place of the native marrow.[22] However, the above theories have since been replaced by the more widely adopted mechanism of pro-inflammatory cytokine surge secondary to rapid accumulation of the neutrophils.[2,3,23] This "engraftment" likely causes a constellation of inflammatory symptoms as defined by the criteria from Spitzer, et al.[10]

The first mention of aGVHD was originally from Bekkum, et al, in 1956 who described a "secondary disease" after an infusion of allogenic bone marrow stem cells into mice that underwent high dose radiation with resulting bone marrow aplasia termed "primary disease." The "secondary disease" was attributed to the donor T lymphocytes that attacked the host's tissue.[24] Since the time of its discovery, various methods have been created to prevent or alleviate the aGVHD, such as the addition of aGVHD prophylaxis regimens and T cell depletion methods as well as the development of new agents to treat aGVHD.[25,26] However, despite all these new developments, high dose steroids remain one of the top choices for aGVHD treatment.[27] Nevertheless, it can be challenging to distinguish aGVHD from engraftment syndrome since the 2 display similar features and onset.[10,28]

Our analysis suggested that ES and aGVHD are closely intertwined, with the increasing diagnosis of aGVHD in patients with ES. This likely reflects the closely linked pathophysiology and association with neutrophil function.[2,29] There is still ongoing research regarding ES on a molecular and cellular level to further characterize the signal pathway of ES and to find methods to minimize the effects as a way of improving transplantation outcome.

According to this regression meta-analysis, differences in stem cell source and aGVHD prophylaxis regimen potentially had effect modification to the association between ES and aGVHD, which could be used to identify high-risk population. Therefore, the team concluded that ES is significantly associated with aGVHD which is concordant with the findings from past studies.[15,17-20] There had been inhomogeneous outcome in terms of subgroup analysis by graft type and aGVHD prophylaxis regimen,[14-21] but according to our analysis, this observed association was stronger among studies that used UC for stem cell source and CsA as aGVHD prophylaxis regimen.

Limitations

There are some limitations to this study. First, the team only included 8 eligible studies. This could possibly limit the external validity of this meta-analysis. Secondly, the team included studies with patients of all ages with various indications for transplant, diverse pre-transplant co-morbidities as well as patients with various disease statuses. These differences could account for the heterogeneity of our outcome. Moreover, the team realized that ES and aGVHD are closely related and that the diagnosis of the 2 entities requires expert opinion and extensive workup which might vary between institutions. And lastly, the team recognizes that, due to the nature of both ES and aGVHD that require treatment with aggressive steroids, patients treated for ES might be under-diagnosed for early aGVHD, therefore underestimating the result.[30-33]

Conclusion

Our meta-analysis of observational studies demonstrated that ES is significantly associated with aGVHD, with nearly 3 times the odds of developing aGVHD in the ES group when compared to the control group. This effect also persisted on the subgroup analyses in regards to stem cell source and aGVHD prophylaxis regimen suggesting that this outcome is unlikely to be casual. Thus, there is a need for further research to optimize the transplant protocols and circumvent these complications. We suggest that further large, prospective, controlled trials are warranted to investigate the finer details of the proposed association between ES and aGVHD.

Conflict of Interest

None of the authors identify a conflict of interest.

Authors' Affiliations:
- Internal Medicine Residency Program, John A. Burns School of Medicine, University of Hawai'i, Honolulu, HI (KP, JK, NL)
- Faculty of medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand (CP)

Correspondence to:
Kittika Poonsombudlert MD; University of Hawai'i Internal Medicine Residency Program, 1356 Lusitana St., 7th floor, Honolulu, HI, 96813; Email: kit7@hawaii.edu

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