Evaluation of effectiveness of hematopoietic stem cell transplantation for the treatment of patients with primary immunodeficiencies: a comprehensive systematic review and meta-analysis 1968-2017.

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Abstract

Background: Hematopoietic stem cell transplantation (HSCT) is the only available treatment with curative potential for patients with primary immunodeficiencies (PID). The effectiveness results measured in terms of overall survival (OS) and event-free survival (EFS) have improved markedly, however, there is a high heterogeneity in those results according to type of PID and when and where the transplant is performed. Despite its clinical importance in the decision-making process on whether to perform the transplant or not, a systematic evaluation of the effectiveness in these patients has never been made.

Objectives: To evaluate the effectiveness of HSCT in patients with PID reported in the scientific literature and its relation with variables of type of disease, year of publication, region and age of the transplant.

Methods: systematic review and meta-analysis with random effects model. In 9 databases, with 36 different search strategies. The exhaustivity and evaluation of the methodological quality was guaranteed. Studies were described with frequencies, the effectiveness meta-analyzed for OS and EFS in all studies, and specifically according to type of PID, continent, sex, donor compatibility and age of the transplant. Meta-regression was carried out to know the change in effectiveness over time. In the meta-analyzes heterogeneity was evaluated with I2 and Cochrane Q test and sensitivity with elimination of each article independently, the confidence was 95%.

Results: A total of 135 articles with complete information on the effectiveness of HSCT in 5259 patients with PID were included; most patients were reported in Europe, North America, and Asia. The main justifications for the transplant were the presence of infections, phenotypic confirmation and genetic diagnosis. The most frequent complications were acute graft versus host disease (GVHD) and infections. The cumulative OS and EFS was 67% (CI 65-69) and 59% (CI 54-63%), respectively. Survival has increased 3% every year. Survival after the first years of transplantation seems to be stable. No differences were found in survival by sex or donor compatibility. Patients who survived the procedure were diagnosed and transplanted earlier and had to wait less time to receive the transplant after being diagnosed than the patients who died.

Conclusion: HSCT is an increasingly effective procedure for the treatment of PID. The decision to perform the transplant should be made as soon as the phenotypic confirmation of the PID is taken, to avoid the risk of complications and increase the probability of survival.

Keywords: Hematopoietic stem cell transplantation, primary immunodeficiencies, effectiveness, systematic review, meta-analysis.

Introduction

Primary immunodeficiencies (PID) or innate errors of immunity are a heterogeneous group of inherited diseases that affect the immune system in number or function, and are characterized by predisposition to recurrent infections, autoimmunity, allergies and cancer (1). More than 400 genetic defects have been associated with PID. The International Union of Immunological Societies (IUIS) PID expert committee every 2 years update the classification of PID in 10 groups according to their genetic defect, clinical, and immunological characteristics (2).

PID are considered as rare diseases, however their prevalence and incidence are not well known. Previous reports had estimated incidence ranging from 1 in 1000 to 1 in 5000 births (3), recent results even suggest that about 1-2% of the word population may be affected by any kind of PID (4). Regardless of this uncertainty, the number of new recognized PID as well as new diagnosed patients increase exponentially every year, and this represents a continuous challenge in terms of medical awareness and treatment approaches for new patients (2,5). Range of clinical manifestation oscillates from life threatening conditions to mild non-severe complications. Long-term complications are frequent, and health related quality of life is markedly lower compared to general population (6–8). Mortality rate among PID patients has been reported between 12% and 30% (9–13), but in the case of severe combined immunodeficiency (SCID), the most life-threatening group of diseases, this is habitually fatal if not treated within the first year of life (14).

Hematopoietic stem cell transplantation (HSCT) is the only treatment with curative capacity for most PID (15). Consist in the replacement of the bone marrow of the patient with a healthy stem cell isolated from a donor (16). The PID field has been pioneer in the development of HSCT since 1968 and nowadays it is broadly applied to treat PID. According to the Jeffrey Modell Foundation 2018 report, only during that year 4421 PID patients received HSCT worldwide, and this represented 113% of increase compared with 2013 (5). This procedure is high-cost and involves intrinsic complications such as immunosuppression, cytotoxicity, graft failure, graft versus host disease (GVHD), susceptibility to infections, among others. HSCT effectiveness is measured in terms of overall survival (OS) and event free survival (EFS). Currently, studies show how effectiveness of transplantation in PID had improved constantly, with OS reaching 90% in SCID patients transplanted mainly in Europe centers (17,18), but at the same time, others, report outcomes below 30% in these patients (19,20). In the same way, with non-SCID disease results are even wider having outcomes as low as 13% up to more than 90% (21,22). This reveals a wide-ranging spectrum and inconsistent results of effectiveness reported for PID patients.

There is no consensus among experts about which non-SCID should be treated with HSCT. The guidelines for HSCT in PID of the Inborn Errors Working Party group, which is part of the European Society for Blood and Marrow Transplantation, describe protocols for the most frequent PID, but do not included indications for a wide range of diseases (23). Castagnoli *et al*, segregates the indications of HSCT according to whether the procedure is "recommended", "partially curative" or "controversial" (24). Most of these indications are also suggested by Mitchell *et al* but the recommendation group for some diseases does not match (25). Additionally, the benefits of HSCT in non-SCID are still controversial. For example, some studies in patients with chronic granulomatous disease (CGD) or CD40 ligand

deficiency (CD40L) under prophylactic treatment, survival was similar to those who undergo HSCT, however, transplanted patients had better quality of life and non-dependence on medications (26–28). There are less reports of effectiveness in non-SCID compared with SCID patients, and they share important limitations as low sample size, and in some cases, no separation of results by disease type. Added to this, the large amount of diseases within this group makes hard to justify a transplant and to know the effectiveness desegregate for type of non-SCID disease which is necessary to facilitate informed decision process to physicians, patients, and their families (18,25).

The available literature presents heterogeneity in relation to the factors that improve the effectiveness of the transplant. Age of transplantation, donor compatibility, sex, type of PID or year of transplantation have been associated but their effect size is not clearly stablished (15,17,18,25). Other variables that are important and frequently reported in the results of HSCT, but have not shown association, are the source of stem cells (peripheral blood, bone marrow or umbilical cord), family or unrelated compatible donor and conditioning regimen (17,23,29). The difference in effectiveness by region where the procedure is performed has not been evaluated.

Despite being a rare disease, great effort has been made to report an increasing number of originals studies and narrative reviews of HSCT in PID, but no effort has been made to date to do a systematic evaluation of the available evidence and assess cumulative effectiveness, indications and main complications of HSCT as treatment of patients with PID. This is not the case for other diseases such as leukemia, Hodgkin lymphoma, Sickle cell disease, leukodystrophy, systemic lupus erythematosus, and antiphospholipid syndrome, where HSCT is also the main therapeutic option, but in which the results of effectiveness have been evaluated with several systematic reviews (30–37).

The aim of this systematic review was evaluate the available evidence on the effectiveness of HSCT and the associated factors for the treatment of patients with PID. We hope that this systematization will be useful for taking informed decisions and to help identify priorities and challenges in the treatment of patients with PID worldwide.

Material and methods

Study design

Systematic review and meta-analysis.

PICO question

Population: all PID patients who have undergone HSCT

Intervention: HSCT

Comparator: none

Outcomes: primary, OS and secondary, EFS

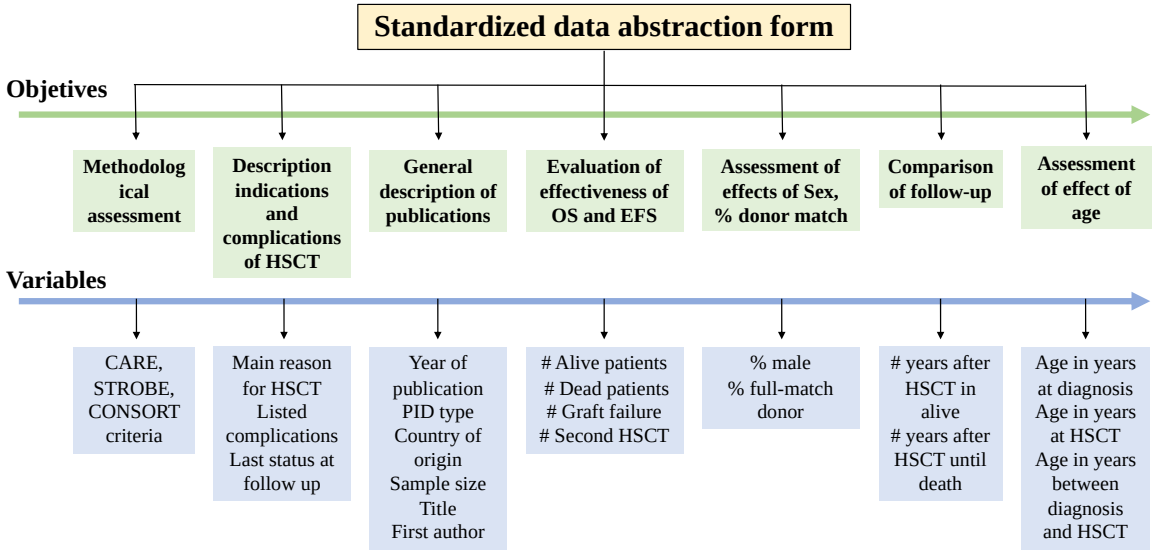
Search and selection protocol according to PRISMA and Cochrane recommendations

Identification: This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) and Cochrane recommendations (38,39). A broad scope research was conducted in order to identify, first all reports of PID, and then select all records related to transplant. We performed electronic searches of Pubmed, Embase, Scopus, Science Direct, Web of Science, Ovid, Cochrane, Lilacs, and Scielo from inception until April 2017. There are no mesh terms for PID, so we used the "Pearl harvesting" method to include all possible terms with which this group of diseases are referred to; the following terms were used: primary, congenital, hereditary, genetic, inborn, innate, heritable, and inherited; each term combined individually with: immunodeficiency, immunodeficiencies, "immune deficiency", and "immune deficiencies"; also, specific terms were included: "immunodeficiency disorder", "immune deficiency disorder", "Inborn error of immunity", and "Inborn errors of immunity", for a total of 36 different search strategies in each of 9 databases mentioned (supplementary material S1). Most articles were captured using an independent search strategy, compared to extensive syntax using OR.

Screening: To ensure exhaustivity, no time, language or study design limits were applied. Only records with PID keywords in title or abstract were considered. Search results were stored in a common source in Zotero; after removing duplicates, the articles containing these key words in tittle or abstract were screened: "transplant", or "trasplant", or "HSCT", or "BMT". Reviews, abstracts, conference or congress abstracts, commentaries, editorials, letters, opinions, notes, books, non-PID related, and not full text available were not included.

Eligibility: The full text of the remaining articles was read, and only articles that evaluated the effectiveness of HSCT, were made in humans, reported full information of effectiveness, and were not previously reported were included for synthesis.

Inclusion: Variables were collected in an excel format, the details of the study (study design, year of publication, first author, country where the study was conducted, continent, and study design); patient characteristics (always separated for living and dead patients: sample size, male percentage, PID disease, PID group and mean and standard deviation for: age of diagnosis and age of transplant; medians were converted to means to pool results following the method described by Luo et al. (40); effectiveness results (OS, defined as the proportion of patients alive at the last follow-up after HCST, and EFS, defined as the proportion of patients alive at the last follow-up without the occurrence of graft rejection and / or need for a second transplant) ; characteristics of the transplant (main justification for HSCT, proportion of full-match donors, recruitment time, main complications after HSCT, and follow-up time) (supplementary material S2).



Schematic representation of extracted variables.

Methodological assessment

Methodological assessment of included studies was assessed using: The 25-criteria the Consolidated Standards of Reporting Trials (CONSORT) (41) for clinical studies, 22-criteria of Strengthening the Reporting of Observational studies in Epidemiology (STROBE) (42) for observational studies, and the 30-criteria of Consensus-based Clinical Case Reporting (CARE) (43) for case reports. Fulfillment of 70% or more of the criteria was considered as a good methodological quality study. Although these guides were published from 2007 onwards, and generally considered an editorial tool, they contain criteria that allow the evaluation of the methodological quality (internal and external validity) of each type of study included in this review.

Data analysis

To describe the general characteristics of the publications included, absolute and relative frequencies of number of studies and number of patients were used. The classification of the type of study design was based on the work of Röhrig 2009 (44), and the classification of the PID group was made based on the IUIS 2017 report (2). The main indications as well as the main complications of HSCT were systematized from the information of case reports.

Given the variability of the studies, all meta-analysis were done under the random effects model. Publication bias was assessed using Funnel plot and Begg's test. Heterogeneity was tested using Cochrane Q test and I^2. Sensitivity analysis for each result was performed by eliminating the studies (one at a time) and verifying if there was a change in the estimate or significance. To evaluate the effectiveness, pooled proportions of OS and EFS were calculated, and subgroup analyzes by type of PID and study continent were made, in which the subgroup and not the study were considered as the unit of analysis, in such case, at least 2 patients in each subgroup were required to calculate the 95% Confidence Interval (CI).

Meta-regression was performed to compare the change in effectiveness according to the year of publication, and to confirm true association of significant variables. The effect of sex and donor compatibility on OS were assessed using Odss ratios of live versus dead SCID and non-SCID patients. To assess overall time of survival, and average time of death after the transplant, the combined mean in years of follow up was calculated, and the results were compared between SCID and non-SCID patients; meta-regression was conducted to assess the change in survival over time after the transplant.

In order to determine the effect of age on the survival of the transplant, in SCID and non-SCID patients, the mean age of diagnosis, mean age of treatment and mean of waiting time to receive the transplant, were compared between living patients and deceased patients, the difference in means was calculated by subtracting the mean age of dead patients from the mean age of alive patients.

Comprehensive Meta-analysis (free trial) was used for analysis (45). P value of 0.05 or less was considered statistically significant. All CI presented are at 95% confidence.

Results

Study Selection

A total of 45,479 studies containing the search terms in title or abstract were identified. After discarding duplicates and studies that did not meet inclusion criteria, 231 were evaluated. 135 studies reported complete information on the effectiveness of HSCT in PID and were included in the qualitative synthesis, and 76 for meta- analysis (Figure 1).

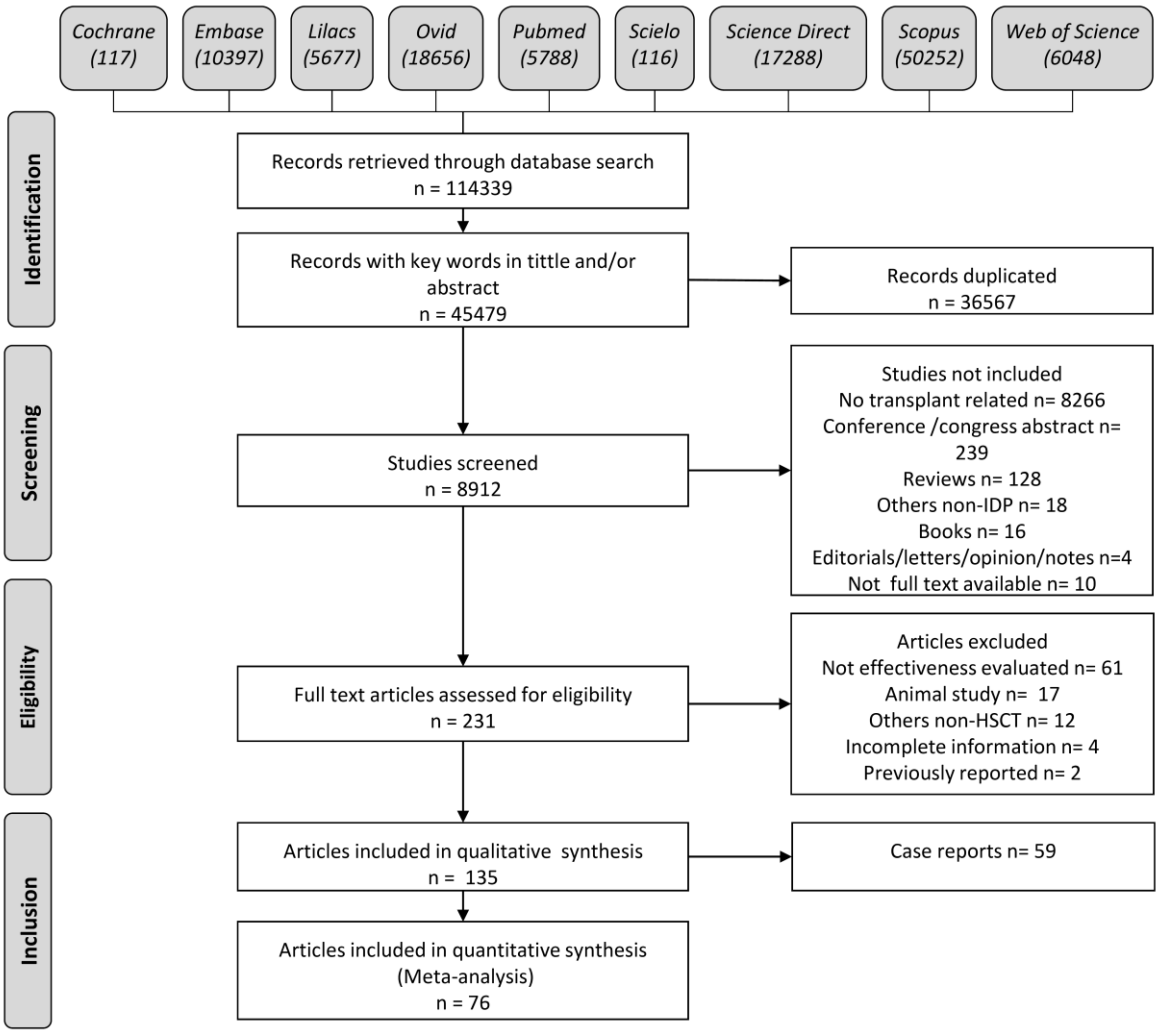


Figure 1. flow diagram for search and selection protocol

Methodological assessment

In 80% (46) of the case report studies, all the methodological criteria of the CARE guide were met. The other 20% met between 43% and 67% of the criteria. None of the studies included the word “case report” as part of keywords, none evaluated the tolerability and adherence to the transplant, and none inquired about the patient's perspective. The least reported items were, prognosis of the disease, use of “case report” in title, report of demographic characteristics of patients and request for informed consent (figure 2A).

In 80% (52) of the observational studies, all the methodological criteria of the STROBE guide were met. The other 20% met between 9% and 68% of the criteria. The least reported items were, statement of limitations, source of funding, and bias control methods (Figure 2B).

Only one of the seven clinical trials met at least 70% of the methodological criteria of the CONSORT guide. The other six partially met between 40% and 68% of the criteria. Given

the nature of this intervention, none of the trials were randomized or blinded, which is why the least reported items were randomization and blinding. However, patient and intervention information were reported almost completely. Few studies declared limitations or specified in the title that it was a clinical trial (Figure 2C).

It should be noted that these guidelines were only incorporated as of 2007, for which studies published before the date should not specify compliance with these criteria

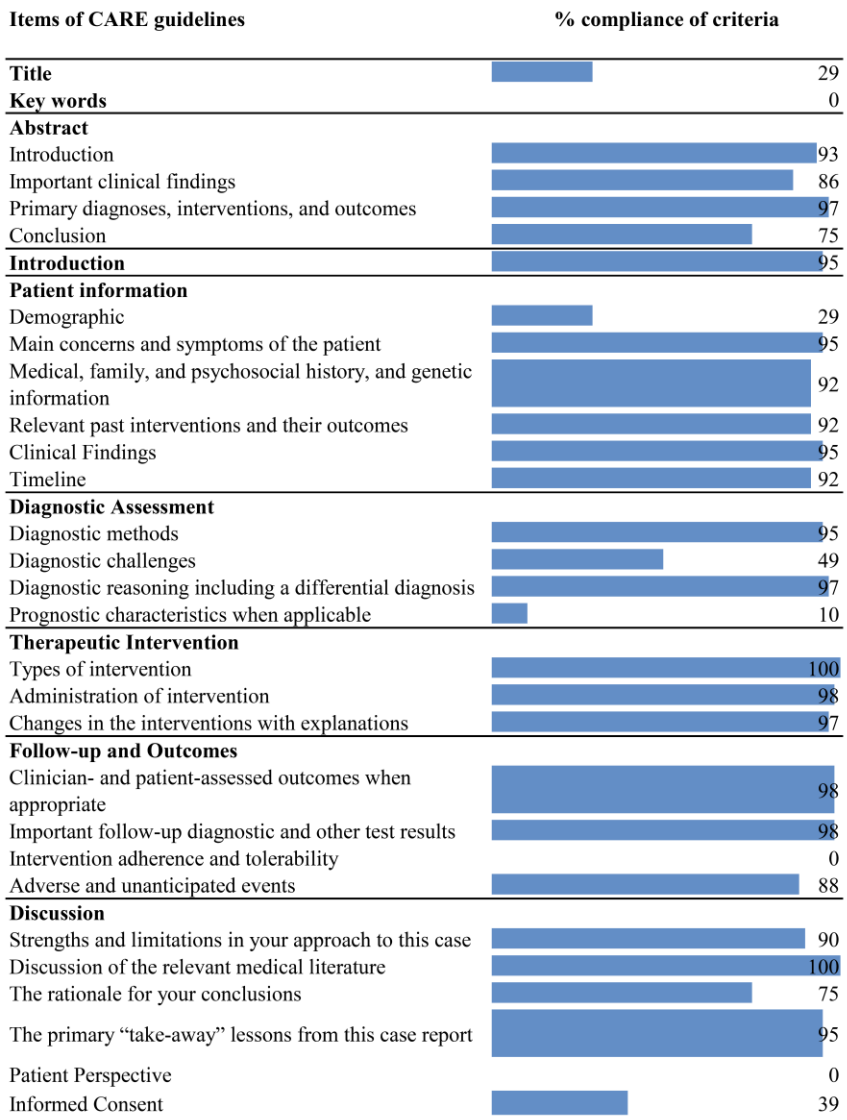


Figure 2A. Proportion of case studies that complied with CARE guidelines

Items of STROBE guidelines	% compliance of criteria
Title and abstract	82
Background/rationale	89
Objectives	58
Methods	
Study design	50
Setting	88
Participants	87
Variables	61
Data sources/ measurement	80
Bias	47
Study size	88
Quantitative variables	86
Statistical methods	53
Results	
Participants	83
Descriptive data	86
Outcome data	87
Main results	88
Other analyses	53
Discussion	
Key results	84
Limitations	28
Interpretation	83
Generalisability	80
Funding	34

Figure 2B. Proportion of observational studies that complied with STROBE criteria

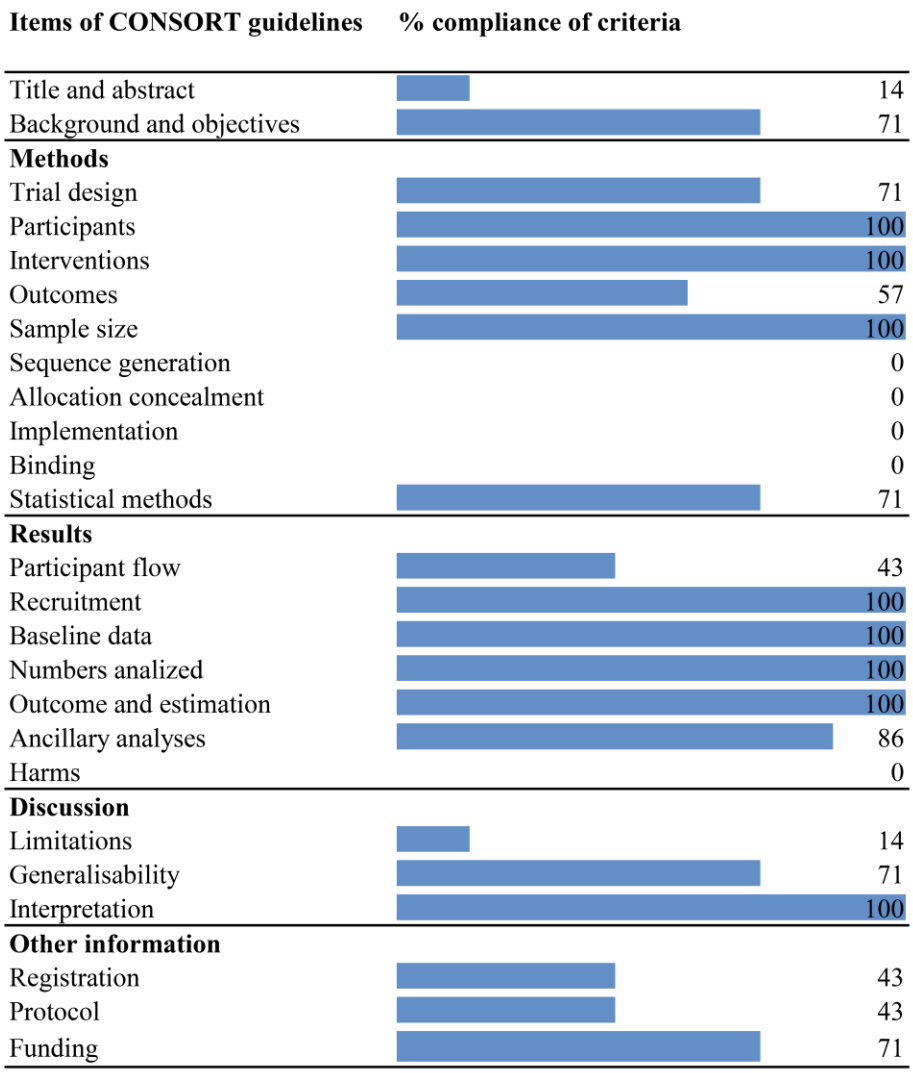


Figure 2C. Proportion of observational studies that complied with CONSORT criteria

Figure 2. Methodological quality assessment. A) CARE, B) STROBE, C) CONSORT.

General characteristics of included articles

A total of 135 studies were included (5259 patients) (table 1). In 50% of reports were published in the last decade, 36% between 2000 and 2009, and only 14% were reported before 2000.

HSCT was indicated in more than 38 different phenotypes which were grouped into nine groups following the classification of the IUIS. In 21 articles (851 patients), the type of PID was not specified, therefore, they were classified as “not specified” (NS).

Table 1. Qualitative syntesis of included studies

Variable	Subgroup	# Studies	%	# Patients	%	Reference
Year of publication						
	1985 - 1999	19	14	502	10	(46–64)
	2000 - 2009	48	36	1728	33	(65–112)
	2010 - 2017	68	50	3029	58	(15,19–21,28,29,113–118,118–173)
	Total	135	100	5259	100	
PID Group						
Antibody deficiencies	CVID	6	2	33	1	(19,72,86,123,155,155)
CID 1	WAS, DGS, CID, CHH, AT, NBS, CHARGE	45	17	670	13	(15,19,21,46,47,50–53,55,56,61,62,67–69,72,74,78,80,81,83,84,86,87,96,102,106,107,113,121,125,129–132,135–139,142,158,164,168)
CID 2	HIES, VODI, NEMO, DKC, PNP, ORAI1	10	4	18	0,3	(53,55,99,108,120,137,139,141,154,169)
Dysregulation	HLH, IPEX, XLP, GS, ITK, CHS, ALPS, CD25, LRBA	33	13	414	8	(15,19,21,52,53,55,67,69,72,78,80,81,83,86,88,97,113,121,124,125,131,135–137,139,141,142,147,148,150,152,157)
Intrinsic defects	OP, STAT1 GOF, WHIM, IFNGR1	7	3	34	1	(47,55,56,109,121,131,174)
Not Specified	PID	21	8	851	16	(21,53,55,64,70,71,79,82,86,89,94,113,119,126,128,130,133,135,137,141,144)
Phagocyte defects	CGD, LAD, SCN, GATA2	45	17	324	6	(15,21,53,55,59,60,63,69,72,78,80,81,86,88,95,103–105,115,117,123,129–132,134–137,139,140,142,143,156,159–163,165–167,170,171,175)
SCID 1	SCID	51	20	2253	43	(15,19,20,29,46–52,55,56,67–69,72–78,80,81,84–88,93,98,111–113,123,125,127,129–132,135–137,139,142,146,153,173,175,176)
SCID 2	CD40L, OS, ZAP70, DOCK8, MHCII, MAGT1	42	16	662	13	(15,19,28,47,53–55,57,58,65–

						69,72,74,78,81,86–88,90,100,101,110,113,114,116,118,122,123,125,127,131,136,139,141–143,145,149,151,172,175)
	Total	260 *	100	5259	100	
Study design	Case report	59	44	81	2	(57–64,90,93–112,145–172,174,176)
	Case series	3	2	16	0	(88,117,120)
	Clinical study	7	5	111	2	(19,67,72,113,131,134,141)
	Cohort	7	5	263	5	(28,47,71,76,114,115,128)
	Descriptive cohort	56	41	3583	68	(15,20,21,29,46,48–52,54–56,65,66,68–70,74,75,77–79,81–87,89,116,118,119,122–127,129,130,132,133,135–140,142–144,173,175,177)
	Description with registry	3	2	1205	23	(53,73,80)
	Total	135	100	5259	100	

* Number total is superior to 135 due to that a paper might report one o more PID diseases.

CID: combined immunodeficiency; SCID: severe combined immunodeficiency; CVID: common variable immunodeficiency; WAS: Wiskott Aldrich syndrome; DGS: DiGeorge syndrome; CHH: Cartilage Hair Hypoplasia syndrome; AT: Ataxia telangiectasia; NBS: Nijmegen Breakage syndrome; CHARGE: Coloboma, Heart defect, Atresia choanae, Retarded growth and development, Genital hypoplasia, and Ear anomalies syndrome; HIES: hyper IgE syndrome; VODI: Hepatic veno-occlusive disease with immunodeficiency; NEMO: Nuclear factor-kappa B Essential Modulator deficiency; DKC: dyskeratosis congenital; PNP: Purine nucleoside phosphorylase deficiency; ORAI1: ORAI1 deficiency; HLH: Hemophagocytic lymphohistiocytosis; IPEX: immune dysregulation, polyendocrinopathy, enteropathy X-linked; XLP: X-linked lymphoproliferative syndrome; GS: Griscelli syndrome; ITK: Interleukin-2-Inducible T-Cell Kinase deficiency; CHS: Chediak Higashi syndrome; ALPS: Autoimmune Lymphoproliferative syndrome; CD25: CD25 deficiency; LRBA: LPS-responsive beige-like anchor deficiency; OP: osteopetrosis; STAT1 GOF: STAT1 gain of function deficiency; WHIM: Warts, Hypogammaglobulinemia, infections, myelokathexis syndrome; IFNR1: Interferon-γ receptor 1 deficiency; CGD: chronic granulomatous disease; LAD: leukocyte adhesion deficiency; SCN: severe congenital neutropenia; GATA2: GATA-binding factor 2 deficiency; CD40L: CD40 ligand deficiency; OS: omenn syndrome; ZAP70: Zeta-chain-associated protein kinase 70 deficiency; DOCK8: Dedicator of cytokinesis 8 deficiency; MHCII: major histocompatibility complex class II deficiency; MAGT1: magnesium transporter 1 deficiency.

In 20% (51) of reports were on severe combined immunodeficiency group (SCID1), with the highest number of patients who undergoing HSCT (2253). In 17% (45) of papers reported data for combined immunodeficiency I or CID1. Within this group there were 670 patients diagnosed with Wiskott Aldrich syndrome (WAS), DiGeorge syndrome (DGS), cartilage hair hypoplasia syndrome (CHH), ataxia telangiectasia (AT), Nijmegen Breakage syndrome

(NBS), and Coloboma, Heart defect, Atresia choanae, Retarded growth, and development, Genital hypoplasia, and Ear anomalies syndrome (CHARGE).

In 16% (42) of studies focused in combined immunodeficiencies generally less profound than severe combined immunodeficiency or SCID2. Within this group there were 662 patients diagnosed with CD40L, Omenn syndrome (OS), Zeta-chain-associated protein kinase 70 deficiency (ZAP70), dedicator of cytokinesis 8 deficiency (DOCK8), major histocompatibility complex class II deficiency (MHCII), and magnesium transporter 1 deficiency (MAGT1).

In 17% (42) of reports were about congenital defects of phagocytes. 324 patients had diagnoses of chronic granulomatous disease (CGD), leukocyte adhesion deficiency (LAD), severe congenital neutropenia (SCN), and GATA-binding factor 2 deficiency (GATA2).

In 13% (33) of papers focused in the group of immune dysregulations. 414 patients were diagnosed with: hemophagocytic lymphohistiocytosis (HLH), immune dysregulation, poliendocrinopathy, enteropathy X-linked (IPEX), X-linked lymphoproliferative syndrome (XLP), Griscelli syndrome (GS), Interleukin-2-Inducible T-Cell Kinase deficiency (ITK), Chediak Higashi syndrome (CHS), autoimmune lymphoproliferative syndrome (ALPS), CD25 deficiency, and LPS-responsive beige-like anchor deficiency (LRBA).

In 4% (10) of studies were about combined immunodeficiency II or CID2. hyper IgE syndrome (HIES), hepatic veno-occlusive disease with immunodeficiency (VODI), nuclear factor-kappa B essential modulator deficiency (NEMO), congenital dyskeratosis (DKC), purine nucleoside phosphorylase deficiency (PNP), and ORAI1 deficiency (ORAI1) were the diagnoses of 18 patients in this group.

In 3% (7) studies papers reported data for intrinsic and innate immunity group. Which included 34 patients with: osteopetrosis (OP), STAT1 gain of function deficiency (STAT1 GOF), warts, hypogammaglobulinemia, infections, myelokathexis syndrome (WHIM), and Interferon-γ receptor 1 deficiency (IFNR1). In the last place, with only 2% (6) articles had reported information for the group of predominantly antibody deficiencies, all 33 patients with a diagnosis of common variable immunodeficiency (CVID).

Case reports and descriptive cohorts comprise 85% of the publications, in this last design alone, 68% of the patients were reported. Only three articles were descriptions of national registries but in those were reported 23% of patients, seven cohort studies, and three case series completed the list of observational studies included. Seven clinical studies or clinical trials were included; they were carried out to compare the effect of certain factors on the effectiveness of the transplant, but none evaluated the effectiveness of the transplant against another alternative.

Studies from almost all regions were found; 48 publication from Asia (615 patients) 38 studies were made in Europe (3452 patients), 34 more from North America (615), 5 in Australia (170 patients), 5 in South America (14 patients), and only 1 in Africa (20 patients). 4 more studies were carried out in collaboration of several countries (figure 3).

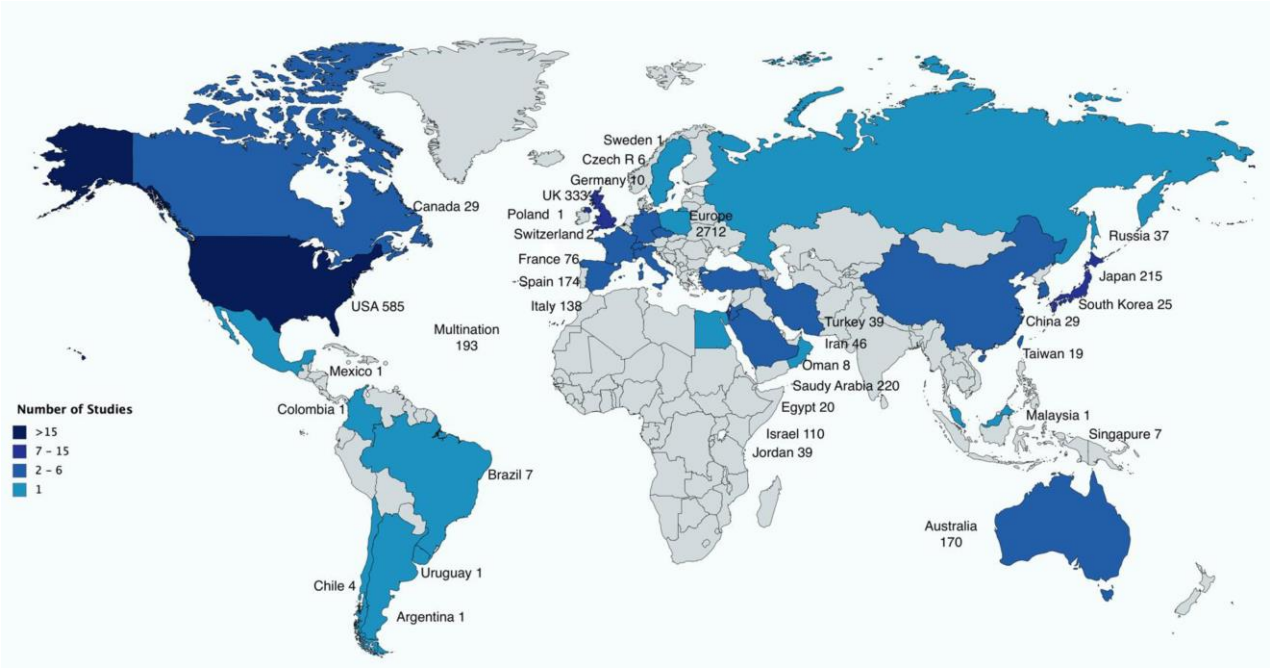


Figure 3. geographical distribution of studies (number of studies per country).

Main indications and complications of HSCT in PID

The indication or justification information of the transplant as well as the list of main complications was obtained from the clinical information of 59 case report studies with 89 patients included (Table 2)

Data were reported for the nine main PID groups. Only 16 (20%) of the patients were women. A varied list of the main decisive justifications for the transplant was found. In 43 (50%) of the cases, the main justification was the presence of infections (mostly of refractory type), genetic and phenotypic confirmation was the next main reason to opt for treatment, other reasons were: risk of damage and organ damage, family history, deterioration of the quality of life among others. 35 patients (40%) presented GVHD, only three cases of chronic type. In 14 patients (20%) there was graft failure and in ten of them a second transplant was performed. In at least 36 patients (40%) there was some type of infection. Despite all the reported complications, only 9 (10%) patients died, four patients are alive but with persistent symptoms, two under immunoglobulin treatment and one was lost follow-up. The other 65 (20%) were reported as alive and well.

Table 2. Description of case reports of HSCT in PID patients.

Study name	Country	PID	PID Group	Sex	Age at diagnosis	Age at HSCT	Main reason for HSCT	HSCT donor	Complications after HSCT	Follow up after	Last status	Reference

										HSCT		
Abu-Arja, R. 2015	USA	CVID	AB DEF	M	5,0	NS	Acute myeloid leukemia	MUD	a GVHD, mucositis	2,0	A & W	
Cambray-Gutierrez, J. 2017	Mexico	CVID	AB DEF	F	15,0	22,0	Refractory infections	MUD	Hypothyroidism and ovarian insufficiency, immune thrombocytopenic purpura, Raynaud's disease and upper respiratory tract persistent infections. 2-3 anual rhinosinusitis	4,0	A + recurrent infections	(155)
Anton-Martin, P. 2016	USA	WAS	CID 1	M	0,0	1,1	Genetic confirmation	MMUD	Acute intraparenchymal hemorrhages	1,0	A & W	(164)
Cohen, J. 2006	United Kingdom	WAS	CID 1	M 2	0,6	0,9	Phenotipic confirmation	MMRD	Graft failure. Second HSCT.	4,0	A & W	
Cohen, J. 2006	United Kingdom	WAS	CID 1	M 2 tween	0,6	1,6	Recurrent infections	MRD	Graft failure, splenectomy for autoimmune hemolytic anemia and thrombocytopenia. Second HSCT (from brother	3,4	A & W	(111)

									and father)			
Dogu, F. 2006	Turkey	WAS	CID 1	M	0,5	2,5	Refractory infections and phenotipic confirmation	MRD	None	3,0	A & W	(178)
Goldsobel, A. 1985	USA	WAS	CID 1	M	NS	10,0	Refractory infections and phenotipic confirmation	MRD	NS	0,8	A & W	(61)
Goldsobel, A. 1985	USA	WAS	CID 1	M	NS	1,4	Refractory infections	MRD	NS	0,8	A & W	
Hourihane, J. 2005	United Kingdom	CID	CID 1	M	6,0	10,0	History of allergies	MMUD	None	2,0	A & W	(96)
Kang, H. 2008	South Korea	WAS	CID 1	M	3,0	NS	Genetic confirmation	MUD	a GVHD, hematuria, proteinuria, hepatic toxicity	1,3	A & W	
Koga, Y. 2014	Japan	WAS	CID 1	M	17,0	NS	Genetic confirmation	MUD	a GVHD Infections for HSV, VZV and, BK virus reactivation	5,0	A & W	(158)
Nakayama, M. 1997	Japan	DGS	CID 1	M	NS	NS	Refractory infections and genetic confirmation	NS	Graft failure. Second HSCT.	NS	A & W	(62)
Slatter, M. 2006	United Kingdom	WAS	CID 1	M	0,2	NS	Genetic confirmation	MUD	Infection for ADV, second cord blood	1,8	A & W	(107)

									unit. a GVHD			
Xiao, J. 2016	China	WAS	CID 1	M	NS	2,7	Refractory infections and genetic confirmation	MMUD	Infection for *Enterococcus faecium*	5,0	A & W	(168)
Gennery, A. 2000	usa	HIES	CID 2	F	1,0	7,0	Refractory infections and quality of life severely decreased	MMUD	a GVHD, infections for HSV, CMV	4,0	A + HIES symptoms	(108)
Myers, L. 2004	USA	PNP	CID 2	M	0,8	3,5	Phenotipic confirmation	MMUD	a GVHD	1,0	A & W	
Singh, V. 2012	United Kingdom	PNP	CID 2	M	1,3	NS	Refractory infections and quality of life severely decreased	MUD	Graft failure. Second HSCT.	1,0	A & W	(169)
Yanagimachi, M. 2016	Japan	HIES	CID 2	F	NS	8,0	Increasing severity of pulmonary infections after lobectomy, quality of life severely decreased	MUD	a GVHD, aspergillosis	8,0	A + recurrent infections	(154)
Yanagimachi, M. 2016	Japan	HIES	CID 2	M	NS	23,0	Risk of pulmonary infections after lobectomy	MRD	Pneumatocele and recurrent bacterial pneumonia	10,0	A + recurrent infections	(154)

Bakhtiar, S. 2017	Germany	LRBA	DYSREGULATION	M	12,0	12,0	Severe enteropathy refractory to immunosuppressive therapy that necessitated parenteral nutrition, as well as the development of autoimmunity	MRD	a GVHD	6,0	A & W	(152)
Hussein, A. 2014	Jordan	HLH	DYSREGULATION	M	19,0	19,0	Genetic confirmation	MRD	None	3,0	A & W	(147)
Jiang, M-Y. 2016	China	XIAP	DYSREGULATION	M	5,8	6,3	NS	MUD	Autoimmune hemolytic anemia and hemorrhagic cystitis	2,5	A & W	(157)
Murguia-Favela, L. 2014	Canada	IPEX	DYSREGULATION	M	NS	1,3	Refractory infections	MUD	None	3,5	A & W	(148)
Rossi, A. 2009	Italy	GS	DYSREGULATION	M	5,0	5,8	NS	MUD	Mucositis, infections for CMV	6,0	A & W	(97)
Tesi, B. 2016	Sweden	LRBA	DYSREGULATION	M	7,0	15,0	Cumulating severe CVID-related clinical problems	MRD	Infections for ADV, RV. Left-side paresis of the facial nerve	2,0	A & W	(150)
Ziegner, U. 2001	USA	XLP	DYSREGULATION	M	0,3	0,7	Death of an older brother with fulminan	MMUD	a GVHD, severe thrombocytopenia, Infection	2,0	A & W	(94)

							t EBV infection		s for VZV			
Ziegner, U. 2001	USA	XLP	DYSREGULATION	M	3,5	4,5	Death of an older brother with fulminant EBV infection	MMUD	a GVHD, infections for VZV	2,0	A & W	(94)
Horwitz, M. 2003	USA	IFNGR1	INTRINSIC	M	NS	5,0	NS	NS	a GVHD, cachexia, metabolic acidosis, azotemia, bronchoconstriction, splenomegaly, and chylous ascites. Fatal polymicrobial sepsis.	1,0	Died	(92)
Reuter, U. 2002	Germany	IFNGR1	INTRINSIC	F	7,0	7,6	Genetic confirmation	MRD	None	4,0	A & W	(109)
Kawano, Y. 1998	Japan	NE	NE	F	NS	1,0	NS	MMRD	None	2,6	A & W	(64)
Bielorai, B. 2000	Israel	CGD	PHAGOCYTE	M	0,3	4,0	Refractory infections	MRD	a GVHD, BK viruria and CMV reactivation	1,3	A & W	(104)
Dediеu, C. 2016	Germany	CGD	PHAGOCYTE	M	0,9	1,2	Refractory infections and phenotipic confirmation	MUD	Infection for RSV	NS	A & W	(171)
Hamidieh, A. 2011	Iran	LAD	PHAGOCYTE	F	5,0	2,5	Refractory infections, phenotipic confirmation and,	MRD	a GVHD, infections for *Pseudomonas spp.*, septicemia.	2,0	A & W	(162)

							failure to thrive					
Hara, K. 2009	Japan	CGD	PHAGOCYTE	M	17,0	NS	Phenotipic confirmation, severe infections	MMUD	Pneumonia and fatal extensive tracheal hemorrhage	0,1	Died	(158)
Ismail, I. 2016	Malaysia	CGD	PHAGOCYTE	M	2,3	7,3	Genetic confirmation	MRD	Mucositis and febrile neutropenia	NS	A & W	(159)
Janda, A. 2012	Czech Republic	CGD	PHAGOCYTE	M	0,5	1,0	Refractory infections	MMUD	a GVHD, ascites, hepatopathy, nephropathy, autoimmune hemolytic anemia. CMV reactivation	3,7	A & W	(166)
Janda, A. 2012	Czech Republic	CGD	PHAGOCYTE	M	1,4	1,8	Refractory infections	MMUD	a GVHD, immune thrombocytopenia and pneumonia	3,5	A & W	(166)
Janda, A. 2012	Czech Republic	CGD	PHAGOCYTE	M	0,5	17,3	Refractory infections	MUD	Fatal Intracranial haemorrhage, CMV reactivation and *Aspergillus calidoustus* brain abses	0,5	Died	(166)
Janda, A. 2012	Czech Republic	CGD	PHAGOCYTE	M	0,5	1,5	Refractory infections	MUD	a GVHD, secundary hypertension	1,0	A & W	(166)
Janda, A. 2012	Czech	CGD	PHAGOCYTE	M	0,6	9,4	Refractory	MMUD	Pancytopenia and	0,8	A & W	(166)

	Republic						infections		catheter sepsis			
Ju, H. 2016	South Korea	CGD	PHAGOCYTE	M	0,8	4,0	Phenotipic confirmation	MRD	Febrile neutropenia, symptomatic pericardial effusion,	2,6	A & W	(165)
Klaudel-Dreszler, M. 2009	Poland	CGD	PHAGOCYTE	M	NS	3,0	Refractory infections and phenotipic confirmation	MUD	Graft failure. Second HSCT. A GVHD, mucositis	3,1	A & W	(105)
Nagler, A. 1999	Israel	CGD	PHAGOCYTE	M	NS	6,0	Refractory infections and phenotipic confirmation	MRD	a GVHD	2,0	A & W	(63)
Oshrine, B. 2015	USA	CGD	PHAGOCYTE	M	0,9	1,1	Phenotipic confirmation	MUD	Graft failure	1,1	A & W	(161)
Oshrine, B. 2015	USA	CGD	PHAGOCYTE	Tween M	2,3	4,0	Phenotipic confirmation, severe infections	MUD	Graft failure, CMV. Second HSCT	0,8	A & W	(161)
Oshrine, B. 2015	USA	CGD	PHAGOCYTE	Tween M	1,8	4,0	Phenotipic confirmation, severe infections	MUD	Graft failure, CMV. Second HSCT	0,7	A & W	(161)
Ozsahin, H. 1998	Switzerland	CGD	PHAGOCYTE	M	0,7	8,0	Refractory infections	MRD	a GVHD	2,0	A & W	(60)
Reichenbach, J. 2008	Switzerland	CGD	PHAGOCYTE	M	0,1	5,6	Refractory infections and genetic confirmation	MRD	Mucositis	2,1	A & W	(95)

Rocha, Y. 2016	Colombia	CGD	PHAGOCYTE	M	0,0	8,0	Refractory infections and genetic confirmation	MRD	Candidiasis	3,0	A & W	(160)
Shigemura, T. 2014	Japan	CGD	PHAGOCYTE	F	0,2	0,3	Phenotipic confirmation	MMUD	Graft failure. Second HSCT. A GVHD, CMV reactivation.	0,8	A & W	(170)
Starý, J. 1996	Czech Republic	LAD	PHAGOCYTE	M	NS	6,0	NS	MUD	none	NS	A & W	(59)
Stepensky, P. 2013	Israel	VPS45	PHAGOCYTE	M	0,6	0,8	Refractory infections	MRD	Pervasive developmental disorder	3,0	A & W	(167)
Stepensky, P. 2013	Israel	VPS45	PHAGOCYTE	M	0,1	1,8	Refractory infections	MMUD	Graft failure. Fatal pulmonary complications	1,0	Died	(167)
Stepensky, P. 2013	Israel	VPS45	PHAGOCYTE	F	0,4	1,0	Refractory infections	MRD	none	0,4	A & W	(167)
Tokunaga, M. 2007	Japan	LAD	PHAGOCYTE	F	0,8	20,0	Refractory infections and quality of life severely decreased	MMUD	c GVHD, mild cystitis, gingivostomatitis	1,8	A & W	(103)
valotti, M. 2015	Japan	CGD	PHAGOCYTE	M	NS	24,0	Refractory infections	MRD	Pulmonary complications	1,0	A & W	(179)
Zhou, L. 2017	China	CDG	PHAGOCYTE	M	6,0	7,0	Genetic confirmation	MMRD	a GVHD, Gastroenterocolitis, aspergillosis and infections for CMV	5,7	A & W	(156)

Alsum, Z. 2012	Saudi Arabia.	SCID	SCID 1	M	1,9	2,0	Refractory infections and genetic confirmation	MRD	Infection for *Cryptococcus neoformans*	0,4	A & W	(146)
Cohen, J. 2006	United Kingdom	SCID	SCID 1	M1	0,5	1,1	Genetic confirmation	MMUD	a GVHD, severe crouplike illness, penicillin-resistant pneumococcal sepsis	8,0	A & W	(111)
Cohen, J. 2006	United Kingdom	SCID	SCID 1	M1 Brother	0,0	0,0	Brother's history	MRD	None	7,0	A & W	(111)
Cuvelier, G. 2009	Canada	SCID	SCID 1	M	0,4	0,5	Phenotipic confirmation	MMUD	Graft failure, fatal severe chronic RSV respiratory disease and extensive chronic GVHD	1,0	Died	(98)
Cuvelier, G. 2009	Canada	SCID	SCID 1	M	0,0	NS	Genetic confirmation and death of an older brother	MMUD	Bacterial sepsis and pyloric stenosis	1,0	A & W	(98)
González, B. 2000	Chile	SCID	SCID 1	M	0,2	0,5	Phenotipic confirmation	MMRD	Fatal pulmonary infections	0,2	Died	(112)
González, B. 2000	Chile	SCID	SCID 1	M	0,3	0,5	Phenotipic confirmation	MRD	a GVHD BCG vaccine dissemination	7,0	A & W	(112)
González, B. 2000	Chile	SCID	SCID 1	M	0,3	0,4	Phenotipic confirmation	MRD	a GVHD	1,0	A & W	(112)
González, B. 2000	Chile	SCID	SCID 1	M	0,7	1,3	Phenotipic confirmation	MMRD	Fatal *S. aureus* sepsis	0,6	Died	(112)

John, T. 2016	USA	SCID	SCID 1	F	NS	18,0	Refractory infections and genetic confirmation	MUD	Gastrointestinal toxicity, infections for norovirus, *Stenotrophomonas maltophilia*, ADV, RV/enterovirus, *Granulicatella adiacens*, EBV	0,6	A + IG	(153)
Ponda, P. 2006	USA	SCID	SCID 1	Tween F	0,5	0,6	Recurrent infections and failure to thrive	MMRD	Fatal chronic lung disease, parainfluenza	1,3	Died	(91)
Ponda, P. 2006	USA	SCID	SCID 1	Tween F	0,5	0,6	Recurrent infections and failure to thrive	MMRD	None	1,8	A + IG	(91)
Trahair, T. 2008	Australia	SCID	SCID 1	F	0,5	0,8	Genetic confirmation	MMUD	a GVHD, VOD, acute renal failure, infections for *Streptpoccal* and *Enterocbacter*	1,7	A & W	(93)
Bonduel, M. 1999	Argentina	MCHII	SCID 2	F	1,1	1,8	Refractory infections, phenotipic confirmation and, failure to thrive	MMRD	Graft failure. Second HSCT, CGVHD, neutropenia, conjuntivitis, infections for *Candida parapsilosis*	2,0	A & W	(58)

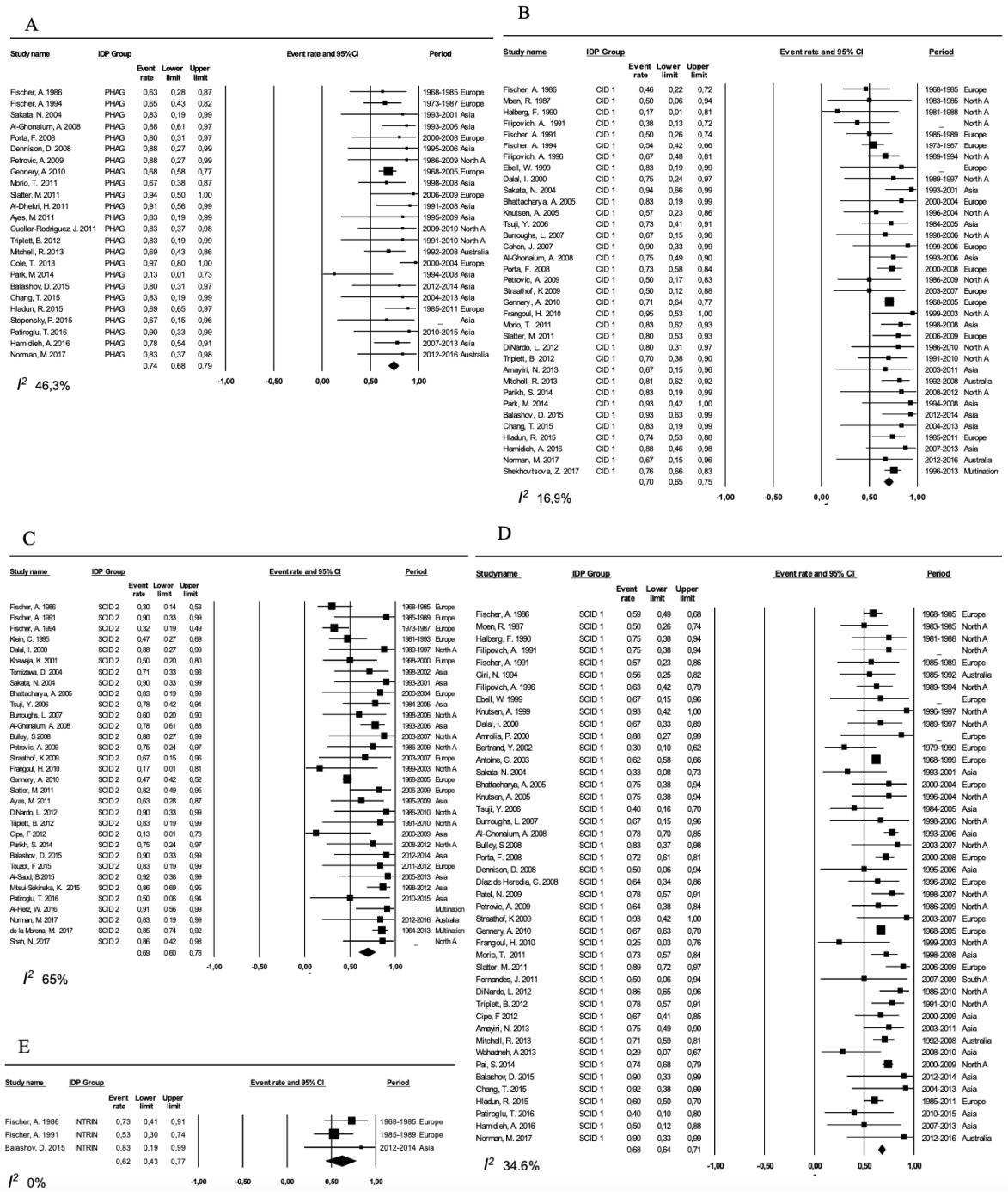
Boztug, H. 2012	Austria	DOCK 8	SCID 2	F	2,5	3,0	Refractory infections and allergies	MUD	a GVHD, Infection for CMV, ADV, HSV1.	0,6	A & W	(145)
Dufort y Álvarez, G. 2011	Uruguay	CD 40L	SCID 2	M	4,0	6,0	High risk of progression to cirrhosis and liver failure, severe growth failure and, recurrent infections.	MRD	a GVHD	2,0	A & W	(151)
Jacobsohn, D. 2004	USA	CD 40L	SCID 2	M	2,0	9,0	High risk of progression to cirrhosis, liver failure and and, poor general health	MRD	HSCT boost	2,0	A & W	(110)
Jacobsohn, D. 2004	USA	CD 40L	SCID 2	M	0,3	5,0	Poor long-term prognosis	MRD	None	2,0	A & W	(110)
Kallen, M. 2015	USA	MC HII	SCID 2	M	0,8	NS	Phenotipic confirmation	MMUD	Graft failure. a GVHD, Infections: coxsackie and echoviral pneumonia, noroviral diarrhea. Fatal acute respiratory distress.	0,3	Died	(180)
Kallen, M. 2015	USA	MC HII	SCID 2	M	1,3	NS	Phenotipic	MMUD	Graft failure, diarrhea,	0,0	Unknown	(180)

							confirmation		vomiting, and mild transaminitis			
Scholl, P. 1998	USA	CD 40L	SCID 2	M	1,4	6,0	Refractory infections and genetic confirmation	MRD	a GVHD, mucositis, Infections for *Streptococcus mitis.*	0,8	A & W	(57)
Schonberger, S. 2009	Germany	OS	SCID 2	F	0,3	6,5	Genetic confirmation	MMUD	a GVHD, recurrent bacterial infections	1,5	A & W	(101)
Tomizawa, D. 2005	Japan	OS	SCID 2	M	0,3	0,6	Genetic confirmation	MMUD	a GVHD, Infection for *Mycobacterium avium*	0,5	A & W	(114)
Ziegner, U. 2001	USA	CD 40L	SCID 2	M	0,0	11,0	NS	MMUD	a GVHD	2,0	A & W	(94)

MRD: match related donor, MUD: match unrelated donor, MMRD: mismatch related donor, MMUD: mismatch unrelated donor. NS: not specified, a GVHD: acute graft versus host disease, c GVHD: chronic graft versus host disease. HSV: Herpes simplex virus, VZV: Varicella zoster virus, ADV: adenovirus, CMV: cytomegalovirus, RV: Rhinovirus, RSV: Respiratory syncytial virus, EBV: Epstein-Barr Virus. A & W: alive and well, IG: Immunoglobulin.

Overall survival

The OS was 67% (CI 65% to 69%) for all diseases combined (using PID subgroup as unit of analysis) I^2 46,3%. In the subgroup analysis by PID type, the best result of OS was for the phagocytic defects with 74% (CI 68-79) (figure 3A), followed by CID1 with 70% (IC 65-75) (figure 3B), SCID 2 with 69% (CI 60-78) (figure 3C), SCID1 with 68% (CI 64-71) (figure 3D), intrinsic defects with 62% (CI 43-77) (figure 3E), dysregulation defects with 58% (CI 53-63) (figure 3F), antibodies deficiency defects with 52% (35 – 69) (figure 3G), and lastly CID2 with 46% (CI 18 -76) (figure 3 H). The not specified PID group had an OS of 72% (CI 64-79) (figure 3 I). These differences were statistically significant (P 0,001). In the sensitivity analysis, any of the removed studies modified the point estimate by more than one unit. There was no evidence of publication bias (P 0,302) (figure 3J)


A
Study name
IDP Group
Event rate
Lower limit
Upper limit
Event rate and 95%CI
Period
Fischer, A 1986 PHAG 0,63 0,28 0,87 1968-1985 Europe
Fischer, A 1994 PHAG 0,65 0,43 0,82 1973-1987 Europe
Sakata, N. 2004 PHAG 0,83 0,19 0,99 1993-2001 Asia
Al-Ghonaium, A. 2008 PHAG 0,88 0,61 0,97 1993-2006 Asia
Porta, F. 2008 PHAG 0,80 0,31 0,97 2000-2008 Europe
Dennison, D. 2008 PHAG 0,88 0,27 0,99 1995-2006 Asia
Petrovic, A. 2009 PHAG 0,88 0,27 0,99 1986-2009 North A
Gennery, A. 2010 PHAG 0,68 0,58 0,77 1968-2005 Europe
Morio, T. 2011 PHAG 0,67 0,38 0,87 1998-2008 Asia
Slatter, M. 2011 PHAG 0,94 0,50 1,00 2006-2009 Europe
Al-Dhekri, H. 2011 PHAG 0,91 0,56 0,99 1991-2008 Asia
Ayas, M. 2011 PHAG 0,83 0,19 0,99 1995-2009 Asia
Cuellar-Rodriguez, J. 2011 PHAG 0,83 0,37 0,98 2009-2010 North A
Triplett, B. 2012 PHAG 0,83 0,19 0,99 1991-2010 North A
Mitchell, R. 2013 PHAG 0,69 0,43 0,86 1992-2008 Australia
Cole, T. 2013 PHAG 0,97 0,80 1,00 2000-2004 Europe
Park, M. 2014 PHAG 0,13 0,01 0,73 1994-2008 Asia
Balashov, D. 2015 PHAG 0,80 0,31 0,97 2012-2014 Asia
Chang, T. 2015 PHAG 0,83 0,19 0,99 2004-2013 Asia
Hladun, R. 2015 PHAG 0,89 0,65 0,97 1985-2011 Europe
Stepensky, P. 2015 PHAG 0,67 0,15 0,96 _ Asia
Patiroglu, T. 2016 PHAG 0,90 0,33 0,99 2010-2015 Asia
Hamidieh, A. 2016 PHAG 0,78 0,54 0,91 2007-2013 Asia
Norman, M 2017 PHAG 0,83 0,37 0,98 2012-2016 Australia
0,74 0,68 0,79
I² 46,3%
-1,00 -0,50 0,00 0,50 1,00
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Study name
IDP Group
Event rate
Lower limit
Upper limit
Event rate and 95% CI
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Halberg, F. 1990 CID 1 0,17 0,01 0,81 1981-1988 North A
Filipovich, A. 1991 CID 1 0,38 0,13 0,72 _ North A
Fischer, A. 1991 CID 1 0,50 0,26 0,74 1985-1989 Europe
Fischer, A. 1994 CID 1 0,54 0,42 0,66 1973-1987 Europe
Filipovich, A. 1996 CID 1 0,67 0,48 0,81 1989-1994 North A
Ebell, W. 1999 CID 1 0,83 0,19 0,99 _ Europe
Dalal, I. 2000 CID 1 0,75 0,24 0,97 1989-1997 North A
Sakata, N. 2004 CID 1 0,94 0,66 0,99 1993-2001 Asia
Bhattacharya, A. 2005 CID 1 0,83 0,19 0,99 2000-2004 Europe
Knutsen, A. 2005 CID 1 0,57 0,23 0,86 1996-2004 North A
Tsuji, Y. 2006 CID 1 0,73 0,41 0,91 1984-2005 Asia
Burroughs, L. 2007 CID 1 0,67 0,15 0,96 1998-2006 North A
Cohen, J. 2007 CID 1 0,90 0,33 0,99 1999-2006 Europe
Al-Ghonaium, A. 2008 CID 1 0,75 0,49 0,90 1993-2006 Asia
Porta, F. 2008 CID 1 0,73 0,58 0,84 2000-2008 Europe
Petrovic, A. 2009 CID 1 0,50 0,17 0,83 1986-2009 North A
Straathof, K 2009 CID 1 0,50 0,12 0,88 2003-2007 Europe
Gennery, A. 2010 CID 1 0,71 0,64 0,77 1968-2005 Europe
Frangoul, H. 2010 CID 1 0,95 0,53 1,00 1999-2003 North A
Morio, T. 2011 CID 1 0,83 0,62 0,93 1998-2008 Asia
Slatter, M. 2011 CID 1 0,80 0,53 0,93 2006-2009 Europe
DiNardo, L. 2012 CID 1 0,80 0,31 0,97 1986-2010 North A
Triplett, B. 2012 CID 1 0,70 0,38 0,90 1991-2010 North A
Amayiri, N. 2013 CID 1 0,67 0,15 0,96 2003-2011 Asia
Mitchell, R. 2013 CID 1 0,81 0,62 0,92 1992-2008 Australia
Parikh, S. 2014 CID 1 0,83 0,19 0,99 2008-2012 North A
Park, M. 2014 CID 1 0,93 0,42 1,00 1994-2008 Asia
Balashov, D. 2015 CID 1 0,93 0,63 0,99 2012-2014 Asia
Chang, T. 2015 CID 1 0,83 0,19 0,99 2004-2013 Asia
Hladun, R. 2015 CID 1 0,74 0,53 0,88 1985-2011 Europe
Hamidieh, A. 2016 CID 1 0,88 0,46 0,98 2007-2013 Asia
Norman, M. 2017 CID 1 0,67 0,15 0,96 2012-2016 Australia
Shekhovtsova, Z. 2017 CID 1 0,76 0,66 0,83 1996-2013 Multination
0,70 0,65 0,75
I² 16,9%
-1,00 -0,50 0,00 0,50 1,00
C
Study name
IDP Group
Event rate
Lower limit
Upper limit
Event rate and 95% CI
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Fischer, A. 1991 SCID 2 0,90 0,33 0,99 1985-1989 Europe
Fischer, A. 1994 SCID 2 0,32 0,19 0,49 1973-1987 Europe
Klein, C. 1995 SCID 2 0,47 0,27 0,69 1981-1993 Europe
Dalal, I. 2000 SCID 2 0,88 0,27 0,99 1989-1997 North A
Khawaja, K. 2001 SCID 2 0,50 0,20 0,80 1998-2000 Europe
Tomizawa, D. 2004 SCID 2 0,71 0,33 0,93 1998-2002 Asia
Sakata, N. 2004 SCID 2 0,90 0,33 0,99 1993-2001 Asia
Bhattacharya, A. 2005 SCID 2 0,83 0,19 0,99 2000-2004 Europe
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Bulley, S 2008 SCID 2 0,88 0,27 0,99 2003-2007 North A
Petrovic, A. 2009 SCID 2 0,75 0,24 0,97 1986-2009 North A
Straathof, K 2009 SCID 2 0,67 0,15 0,96 2003-2007 Europe
Frangoul, H. 2010 SCID 2 0,17 0,01 0,81 1999-2003 North A
Gennery, A. 2010 SCID 2 0,47 0,42 0,52 1998-2005 Europe
Slatter, M. 2011 SCID 2 0,82 0,49 0,95 2006-2009 Europe
Ayas, M. 2011 SCID 2 0,63 0,28 0,87 1995-2009 Asia
DiNardo, L. 2012 SCID 2 0,90 0,33 0,99 1986-2010 North A
Triplett, B. 2012 SCID 2 0,83 0,19 0,99 1991-2010 North A
Cipe, F 2012 SCID 2 0,13 0,01 0,73 2000-2009 Asia
Parikh, S. 2014 SCID 2 0,75 0,24 0,97 2008-2012 North A
Balashov, D. 2015 SCID 2 0,90 0,33 0,99 2012-2014 Asia
Touzot, F 2015 SCID 2 0,83 0,19 0,99 2011-2012 Europe
Al-Saud, B 2015 SCID 2 0,92 0,38 0,99 2005-2013 Asia
Mitsui-Sekinaka, K 2015 SCID 2 0,86 0,69 0,95 1998-2012 Asia
Patiroglu, T. 2016 SCID 2 0,50 0,06 0,94 2010-2015 Asia
Al-Herz, W. 2016 SCID 2 0,91 0,56 0,99 _ Multination
Norman, M. 2017 SCID 2 0,83 0,19 0,99 2012-2016 Australia
de la Morena, M. 2017 SCID 2 0,85 0,74 0,92 1964-2013 Multination
Shah, N. 2017 SCID 2 0,86 0,42 0,98 _ North A
0,69 0,60 0,78
I² 65%
-1,00 -0,50 0,00 0,50 1,00
D
Study name
IDP Group
Event rate
Lower limit
Upper limit
Event rate and 95% CI
Period
Fischer, A. 1986 SCID 1 0,59 0,49 0,68 1968-1985 Europe
Moen, R. 1987 SCID 1 0,50 0,26 0,74 1983-1985 North A
Halberg, F. 1990 SCID 1 0,75 0,38 0,94 1981-1988 North A
Filipovich, A. 1991 SCID 1 0,75 0,38 0,94 _ North A
Fischer, A. 1991 SCID 1 0,57 0,23 0,86 1985-1989 Europe
Giri, N. 1994 SCID 1 0,56 0,25 0,82 1985-1992 Australia
Filipovich, A. 1996 SCID 1 0,63 0,42 0,79 1989-1994 North A
Ebell, W. 1999 SCID 1 0,67 0,15 0,96 _ Europe
Knutsen, A. 1999 SCID 1 0,93 0,42 1,00 1996-1997 North A
Dalal, I. 2000 SCID 1 0,67 0,33 0,89 1989-1997 North A
Amrolia, P. 2000 SCID 1 0,88 0,27 0,99 _ Europe
Bertrand, Y. 2002 SCID 1 0,30 0,10 0,62 1979-1999 Europe
Antoine, C. 2003 SCID 1 0,62 0,58 0,66 1968-1999 Europe
Sakata, N. 2004 SCID 1 0,33 0,08 0,73 1993-2001 Asia
Bhattacharya, A. 2005 SCID 1 0,75 0,38 0,94 2000-2004 Europe
Knutsen, A. 2005 SCID 1 0,75 0,38 0,94 1996-2004 North A
Tsuji, Y. 2006 SCID 1 0,40 0,16 0,70 1984-2005 Asia
Burroughs, L. 2007 SCID 1 0,67 0,15 0,96 1998-2006 North A
Al-Ghonaium, A. 2008 SCID 1 0,78 0,70 0,85 1993-2006 Asia
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Porta, F. 2008 SCID 1 0,72 0,61 0,81 2000-2008 Europe
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Díaz de Heredia, C. 2008 SCID 1 0,64 0,34 0,86 1996-2002 Europe
Patel, N. 2009 SCID 1 0,78 0,57 0,91 1998-2007 North A
Petrovic, A. 2009 SCID 1 0,64 0,38 0,84 1986-2009 North A
Straathof, K 2009 SCID 1 0,93 0,42 1,00 2003-2007 Europe
Gennery, A. 2010 SCID 1 0,67 0,63 0,70 1968-2005 Europe
Frangoul, H. 2010 SCID 1 0,25 0,03 0,76 1999-2003 North A
Morio, T. 2011 SCID 1 0,73 0,57 0,84 1998-2008 Asia
Slatter, M. 2011 SCID 1 0,89 0,72 0,97 2006-2009 Europe
Fernandes, J. 2011 SCID 1 0,50 0,06 0,94 2007-2009 South A
DiNardo, L. 2012 SCID 1 0,86 0,65 0,96 1986-2010 North A
Triplett, B. 2012 SCID 1 0,78 0,57 0,91 1991-2010 North A
Cipe, F 2012 SCID 1 0,67 0,41 0,85 2000-2009 Asia
Amayiri, N. 2013 SCID 1 0,75 0,49 0,90 2003-2011 Asia
Mitchell, R. 2013 SCID 1 0,71 0,59 0,81 1992-2008 Australia
Wahadneh, A 2013 SCID 1 0,29 0,07 0,67 2008-2010 Asia
Pai, S. 2014 SCID 1 0,74 0,68 0,79 2000-2009 North A
Balashov, D. 2015 SCID 1 0,90 0,33 0,99 2012-2014 Asia
Chang, T. 2015 SCID 1 0,92 0,38 0,99 2004-2013 Asia
Hladun, R. 2015 SCID 1 0,60 0,50 0,70 1985-2011 Europe
Patiroglu, T. 2016 SCID 1 0,40 0,10 0,80 2010-2015 Asia
Hamidieh, A. 2016 SCID 1 0,50 0,12 0,88 2007-2013 Asia
Norman, M. 2017 SCID 1 0,90 0,33 0,99 2012-2016 Australia
0,68 0,64 0,71
I² 34.6%
-1,00 -0,50 0,00 0,50 1,00
E
Study name
IDP Group
Event rate
Lower limit
Upper limit
Event rate and 95% CI
Period
Fischer, A. 1986 INTRIN 0,73 0,41 0,91 1968-1985 Europe
Fischer, A. 1991 INTRIN 0,53 0,30 0,74 1985-1989 Europe
Balashov, D. 2015 INTRIN 0,83 0,19 0,99 2012-2014 Asia
0,62 0,43 0,77
I² 0%
-1,00 -0,50 0,00 0,50 1,00

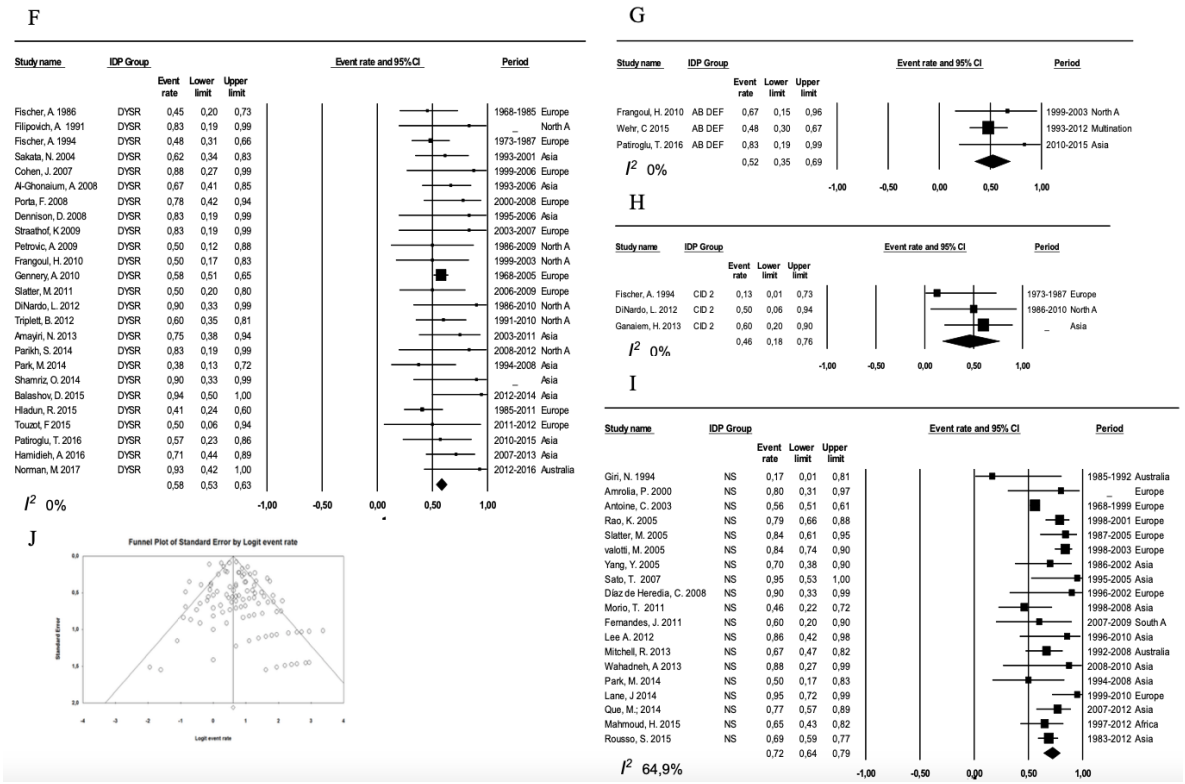


Figure 3. Results of overall survival by PID group

The OS among continents (using study as unit of analysis) was 71% (CI 68 – 73). The OS for transplants performed in multination centers was 75% (CI 57 - 88), followed by results in Asia of 73% (CI 68 - 77), North America 71% (CI 67 - 75), Europe 67% (63 – 72) Africa 65% (CI 43 – 82) and finally South America 65% (43 – 82). These differences were nor statistically significant (P 0,706) (Figure 4 A).

When OS was compared by year of publication, there was a positive regression coefficient of 0,03 (P 0,001), that is, the OS improved 3% every year from the first included report in 1968 until 2017. The OS before 2000s was 54% (CI 50 – 58) and has improved to 74% (CI 70 – 77) after 2010 (figure 4B). In the meta-regression model, PID groups and year of publication, but not continent, remained statistically.

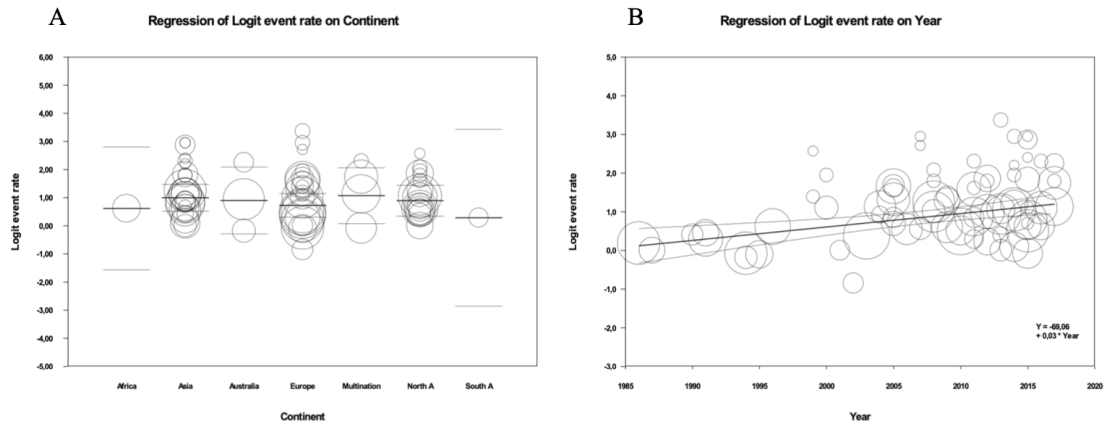


Figure 4. Overall Survival compared by Continent and year of publication

Event-free survival.

EFS was 59% (CI 54 -63) (using PID subgroup as unit of analysis), I^2 *65,7%*. The highest rate of EFS was observed within the dysregulation defects with 88% (CI 50 -99), followed by phagocytic defects with 70% (CI 46 – 87), SCID2 with 64% (CI 39 - 83), CID2 with 60 (CI 20 - 90), SCID1 with 56% (CI 47 – 65), CID1 with 52% (CI 31 - 72) and, lastly, antibodies defects with 44% (CI 26 - 63). Within the not specified PID, the EFS was 60% (CI 54 - 67). There was no significant difference among the disease groups (P 0,428) (figure 5A). When compared by region, the EFS was 59% (53 -64). The best EFS was for patients transplanted in North America with 63% (CI 52 -73), followed by Europe with 62% (CI 49 - 73), Asia with 58% (CI 50 – 66), Australia with 57% (CI 29 - 81), Multination with 56% (CI 37 - 74), Africa with 55% (34 - 75) and South America with 25% (CI 0.8 – 55). These differences were not statistically significant (P 0,435) (figure 5B). The year of publication did not have a significant correlation (P 0,300) (figure 5C). In the meta-regression model, any of the variables had a significant association with EFS. Sensitivity analysis showed not substantial modifications. There was no evidence of publication bias (P 0,138) (figure 5D)

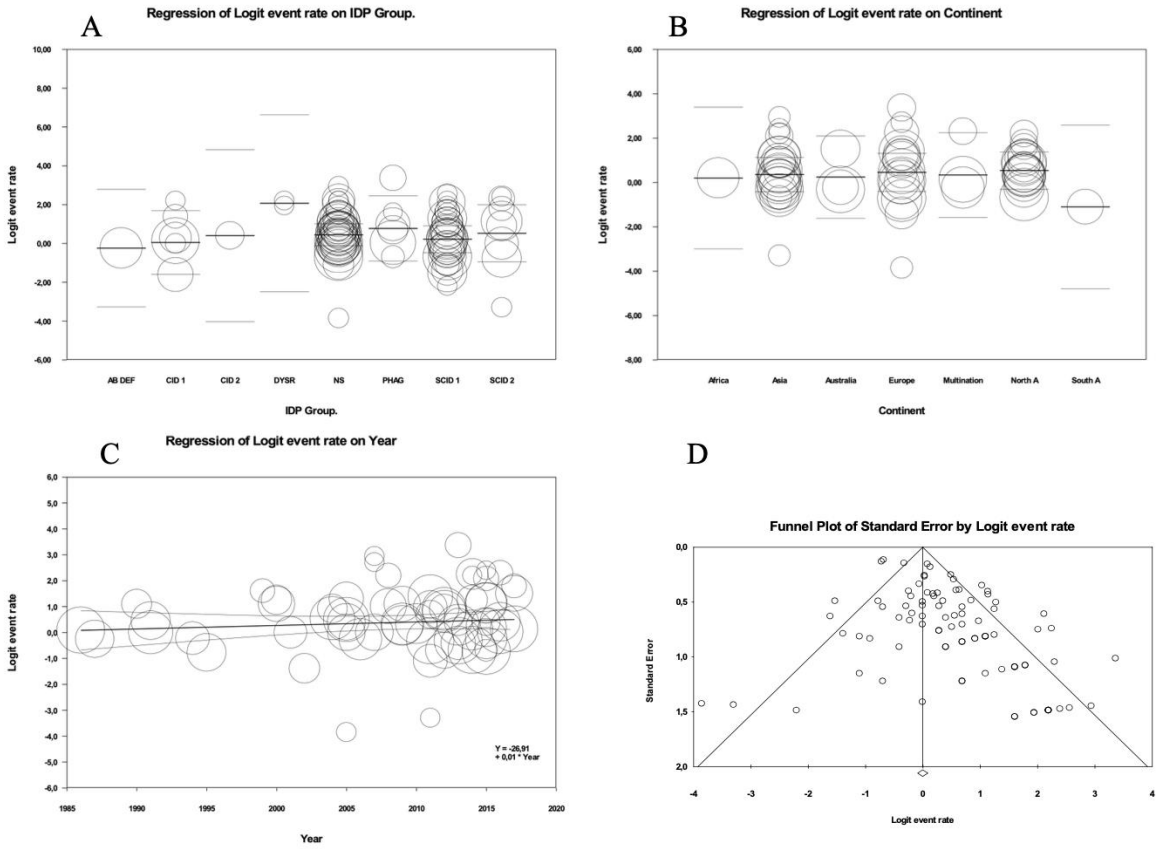


Figure 5. Event Free Survival compared by PID group, continent and year of publication

Comparisons between SCID and non-SCID patients

Subsequent comparisons were made between the SCID and non-SCID patient groups, mainly because non-SCID diseases individually had very little data.

Time of follow up

Patients diagnosed with SCID were followed after HSCT for 3.3 years (CI 1.9 - 4.7) and non-SCID for 4.2 years (CI 3.2 - 5.1). The time in which the patients diagnosed with SCID who did not survive the transplant died was 0.2 years (CI 02 - 0.3) after the procedure and the non-SCID at 0.3 years (CI 0.2 - 0.3). The percentage of survival does not change over time after treatment (P 0.6653), that is, survival behaves stable regardless of the follow-up time (figure 6)

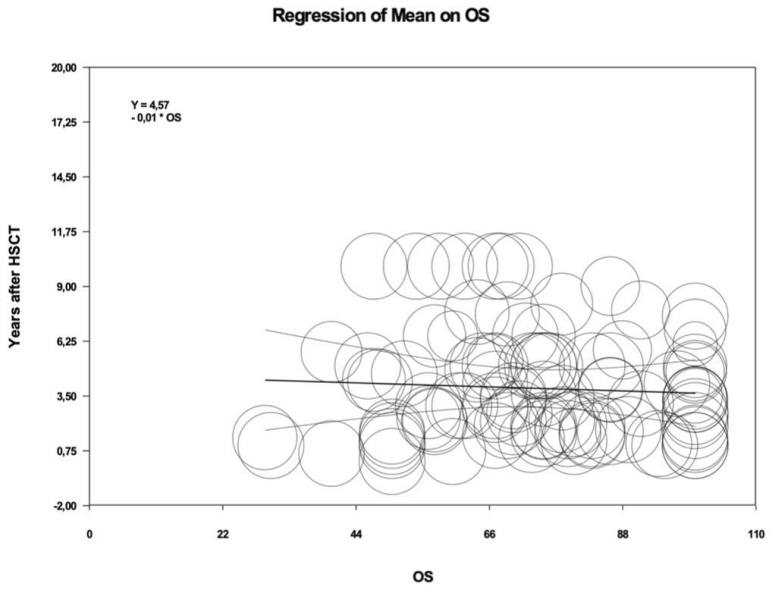


Figure 6. Comparation of years after HCST with proportion of OS.

Donor compatibility and sex.

The proportion of 100% compatible donors was 45% (CI 40-50). There were no significant differences in proportions between non-SCID and SCID patients (P 0.080) or between individuals who survived and those who did not (P 0.161). The proportion of HSCT with a 100% compatible donor shows a tendency to increase over time, however, the correlation was not statistically significant (P 0.0982). The odds ratio for the proportion of men among individuals who survived versus those not on HSCT was not statistically significant in either of the two disease groups (table 3).

Table 3. Summary of male and full match proportion effect on survival

IDP Group	# Studies	Point estimate	Lower limit	Upper limit	Test of null (P value)	Heterogeneity (P value)
Odds ratio male (alive versus dead)						
Non-SCID	19	1,09	0,57	2,08	0,787	0,664
SCID	17	0,77	0,37	1,59	0,474	0,595
Overall	36	0,94	0,58	1,52	0,786	0,729
Odds ratio full match (alive versus dead)						
Non-SCID	23	1,51	1,00	2,30	0,053	0,843
SCID	15	1,10	0,46	2,62	0,832	0,290
Overall	38	1,43	0,98	2,08	0,066	0,691

Age of diagnosis

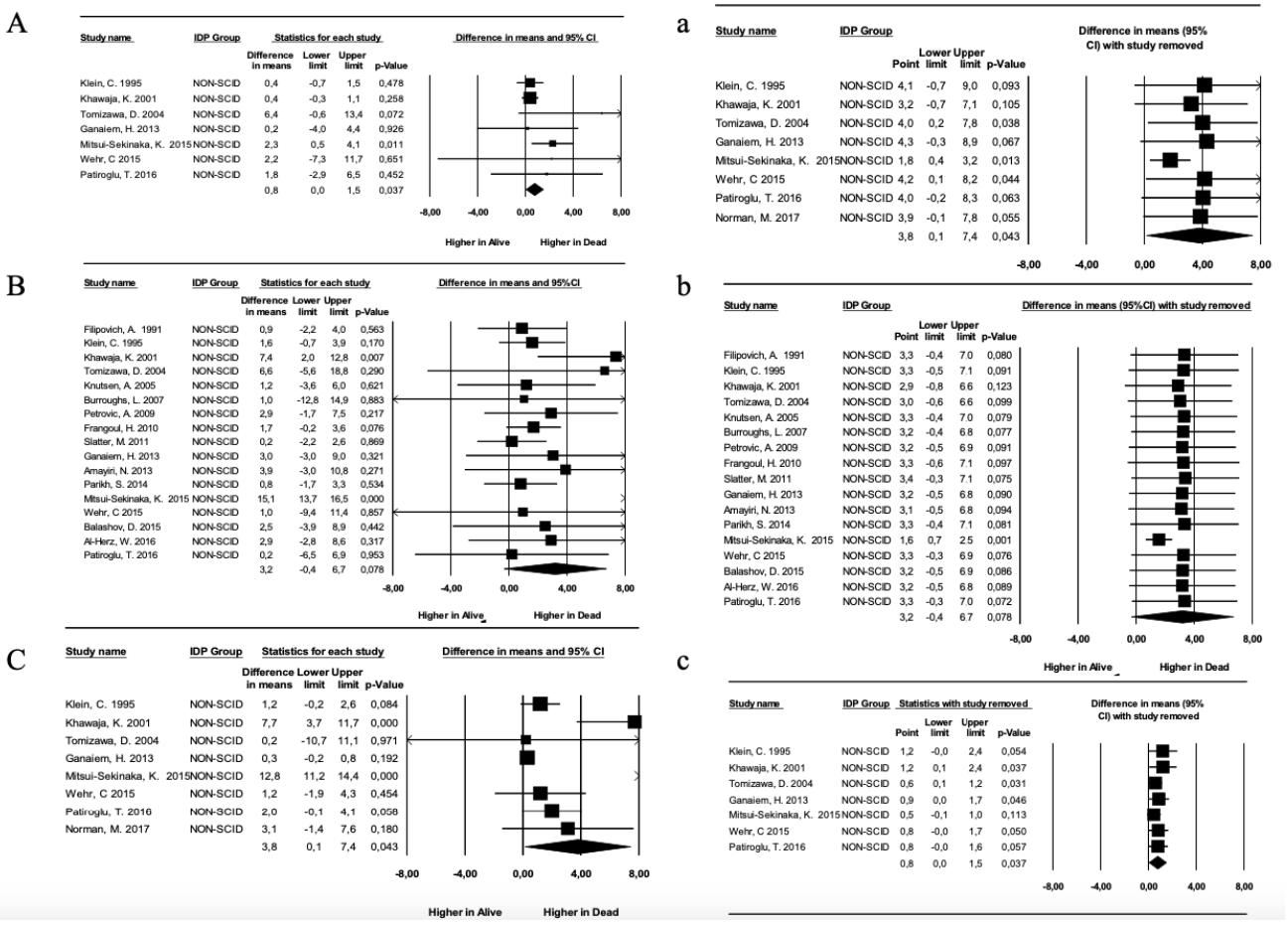
Patients diagnosed with SCID were diagnosed earlier than non-SCID, 0.6 years (CI 0.4 - 0.8) versus 2 years (1.5 - 2.5) in surviving individuals, and 0.3 years (CI 0.2 - 0.4) versus 0.6 years (0.4 - 0.8) in patients who died. In 12 studies reported both, the age of diagnosis in patients who survived, and the age of those who did not survived to HSCT, the differences in mean ages were calculated. Patients who died in the non-SCID group were on average 0.8 years (CI 0.1 - 1.5) older than alive ones (P 0.037) (figure 7A), however, the sensitivity analysis shows the significance is lost by eliminating independently four of the seven studies included in this group (figure 7a). In the case of SCID patients, although dead patients were also older than the survivors, the difference was not significant (P 0.218) (figure 7D) and in the sensitivity analysis the removal of any of the studies affects the point estimate (Figure 6) (figure 7d).

Age of transplant

Patients diagnosed with SCID were transplanted at an earlier age compared to the non-SCID patient group, 0.7 years (CI 0.6 - 0.7) versus 3.1 years (2.7 - 3.6) in the surviving individuals and 0.6 years (CI 0.4 - 0.8) versus 5 years (CI 4.0 - 6.0) in patients who died. 33 studies reported both, the age of diagnosis in patients who survived, and the age of those who did not survived to HSCT. the differences in mean ages were calculated. Patients who died in the non-SCID group were transplanted on average 3.2 years (CI -0.4 - 6.7) later than patients who survived, however, this difference did not reach statistical significance (P 0.078) (figure 7 B) and in the analysis of sensitivity only the removal of 1 of the 17 included studies modified the outcome (figure 7b). In the group of SCID patients, the deceased patients also received the transplant later than the survivors, 0.1 year (CI 0.0 - 0.2) (P 0.043) (figure 7E), however, in the sensitivity analysis the independent removal of 9 of the 16 studies results in loss of the significance found (Figure 7e).

Waiting time between diagnosis and treatment

With the studies that reported both the age of diagnosis and the age of transplant, the time between was calculated to determine the time patients were waiting to receive the transplant. Patients diagnosed with SCID waited for less time compared to the non-SCID patient group 0.3 years (CI 0.2 - 0.4) versus 2.5 years (1.5 - 3.6) in surviving individuals and 0.2 years (CI 0.1 - 0.4) versus 2.6 years (1.8 - 3.4) in patients who died. 13 studies reported both, the age of diagnosis in patients who survived, and the age of those who did not survived to HSCT. the differences in mean ages were calculated. Patients who died in the non-SCID group were waiting on average 3.8 years (CI 0.1 - 7.4) longer than patients who survived (P 0.043) (figure 7C), however, in the sensitivity analysis the independent removal of 5 of the 8 Included studies modified the outcome (figure 7c). In the group of SCID patients, the deceased patients also waited longer to receive the transplant compared to the survivors, 0.1 year (CI -0.1 - 0.3) but this difference was not significant (P 0.159) (figure 7F), and in the sensitivity analysis the removal of None of the 5 included studies modified the outcome (Figure 7f).


A
Study name
IDP Group
Statistics for each study
Difference in means
Lower limit
Upper limit
p-Value
Difference in means and 95% CI
Klein, C. 1995 NON-SCID 0,4 -0,7 1,5 0,478
Khawaja, K. 2001 NON-SCID 0,4 -0,3 1,1 0,258
Tomizawa, D. 2004 NON-SCID 6,4 -0,6 13,4 0,072
Ganaiem, H. 2013 NON-SCID 0,2 -4,0 4,4 0,926
Mitsui-Sekinaka, K. 2015 NON-SCID 2,3 0,5 4,1 0,011
Wehr, C 2015 NON-SCID 2,2 -7,3 11,7 0,651
Patiroglu, T. 2016 NON-SCID 1,8 -2,9 6,5 0,452
0,8 0,0 1,5 0,037
-8,00 -4,00 0,00 4,00 8,00
Higher in Alive
Higher in Dead
a
Study name
IDP Group
Point
Lower limit
Upper limit
p-Value
Difference in means (95% CI) with study removed
Klein, C. 1995 NON-SCID 4,1 -0,7 9,0 0,093
Khawaja, K. 2001 NON-SCID 3,2 -0,7 7,1 0,105
Tomizawa, D. 2004 NON-SCID 4,0 0,2 7,8 0,038
Ganaiem, H. 2013 NON-SCID 4,3 -0,3 8,9 0,067
Mitsui-Sekinaka, K. 2015 NON-SCID 1,8 0,4 3,2 0,013
Wehr, C 2015 NON-SCID 4,2 0,1 8,2 0,044
Patiroglu, T. 2016 NON-SCID 4,0 -0,2 8,3 0,063
Norman, M. 2017 NON-SCID 3,9 -0,1 7,8 0,055
3,8 0,1 7,4 0,043
-8,00 -4,00 0,00 4,00 8,00
B
Study name
IDP Group
Statistics for each study
Difference in means
Lower limit
Upper limit
p-Value
Difference in means and 95%CI
Filipovich, A. 1991 NON-SCID 0,9 -2,2 4,0 0,563
Klein, C. 1995 NON-SCID 1,6 -0,7 3,9 0,170
Khawaja, K. 2001 NON-SCID 7,4 2,0 12,8 0,007
Tomizawa, D. 2004 NON-SCID 6,6 -5,6 18,8 0,290
Knutsen, A. 2005 NON-SCID 1,2 -3,6 6,0 0,621
Burroughs, L. 2007 NON-SCID 1,0 -12,8 14,9 0,883
Petrovic, A. 2009 NON-SCID 2,9 -1,7 7,5 0,217
Frangoul, H. 2010 NON-SCID 1,7 -0,2 3,6 0,076
Slatter, M. 2011 NON-SCID 0,2 -2,2 2,6 0,869
Ganaiem, H. 2013 NON-SCID 3,0 -3,0 9,0 0,321
Amayiri, N. 2013 NON-SCID 3,9 -3,0 10,8 0,271
Parikh, S. 2014 NON-SCID 0,8 -1,7 3,3 0,534
Mitsui-Sekinaka, K. 2015 NON-SCID 15,1 13,7 16,5 0,000
Wehr, C 2015 NON-SCID 1,0 -9,4 11,4 0,857
Balashov, D. 2015 NON-SCID 2,5 -3,9 8,9 0,442
Al-Herz, W. 2016 NON-SCID 2,9 -2,8 8,6 0,317
Patiroglu, T. 2016 NON-SCID 0,2 -6,5 6,9 0,953
3,2 -0,4 6,7 0,078
-8,00 -4,00 0,00 4,00 8,00
Higher in Alive
Higher in Dead
b
Study name
IDP Group
Point
Lower limit
Upper limit
p-Value
Difference in means (95%CI) with study removed
Filipovich, A. 1991 NON-SCID 3,3 -0,4 7.0 0,080
Klein, C. 1995 NON-SCID 3,3 -0,5 7.1 0,091
Khawaja, K. 2001 NON-SCID 2,9 -0,8 6.6 0,123
Tomizawa, D. 2004 NON-SCID 3,0 -0,6 6.6 0,099
Knutsen, A. 2005 NON-SCID 3,3 -0,4 7.0 0,079
Burroughs, L. 2007 NON-SCID 3,2 -0,4 6.8 0,077
Petrovic, A. 2009 NON-SCID 3,2 -0,5 6.9 0,091
Frangoul, H. 2010 NON-SCID 3,3 -0,6 7.1 0,097
Slatter, M. 2011 NON-SCID 3,4 -0,3 7.1 0,075
Ganaiem, H. 2013 NON-SCID 3,2 -0,5 6.8 0,090
Amayiri, N. 2013 NON-SCID 3,1 -0,5 6.8 0,094
Parikh, S. 2014 NON-SCID 3,3 -0,4 7.1 0,081
Mitsui-Sekinaka, K. 2015 NON-SCID 1,6 0,7 2.5 0,001
Wehr, C 2015 NON-SCID 3,3 -0,3 6.9 0,076
Balashov, D. 2015 NON-SCID 3,2 -0,5 6.9 0,086
Al-Herz, W. 2016 NON-SCID 3,2 -0,5 6.8 0,089
Patiroglu, T. 2016 NON-SCID 3,3 -0,3 7.0 0,072
3,2 -0,4 6.7 0,078
-8,00 -4,00 0,00 4,00 8,00
Higher in Alive
Higher in Dead
C
Study name
IDP Group
Statistics for each study
Difference in means
Lower limit
Upper limit
p-Value
Difference in means and 95% CI
Klein, C. 1995 NON-SCID 1,2 -0,2 2,6 0,084
Khawaja, K. 2001 NON-SCID 7,7 3,7 11,7 0,000
Tomizawa, D. 2004 NON-SCID 0,2 -10,7 11,1 0,971
Ganaiem, H. 2013 NON-SCID 0,3 -0,2 0,8 0,192
Mitsui-Sekinaka, K. 2015 NON-SCID 12,8 11,2 14,4 0,000
Wehr, C 2015 NON-SCID 1,2 -1,9 4,3 0,454
Patiroglu, T. 2016 NON-SCID 2,0 -0,1 4,1 0,058
Norman, M. 2017 NON-SCID 3,1 -1,4 7,6 0,180
3,8 0,1 7,4 0,043
-8,00 -4,00 0,00 4,00 8,00
Higher in Alive
Higher in Dead
c
Study name
IDP Group
Statistics with study removed
Point
Lower limit
Upper limit
p-Value
Difference in means (95% CI) with study removed
Klein, C. 1995 NON-SCID 1,2 -0,0 2,4 0,054
Khawaja, K. 2001 NON-SCID 1,2 0,1 2,4 0,037
Tomizawa, D. 2004 NON-SCID 0,6 0,1 1,2 0,031
Ganaiem, H. 2013 NON-SCID 0,9 0,0 1,7 0,046
Mitsui-Sekinaka, K. 2015 NON-SCID 0,5 -0,1 1,0 0,113
Wehr, C 2015 NON-SCID 0,8 -0,0 1,7 0,050
Patiroglu, T. 2016 NON-SCID 0,8 -0,0 1,6 0,057
0,8 0,0 1,5 0,037
-8,00 -4,00 0,00 4,00 8,00

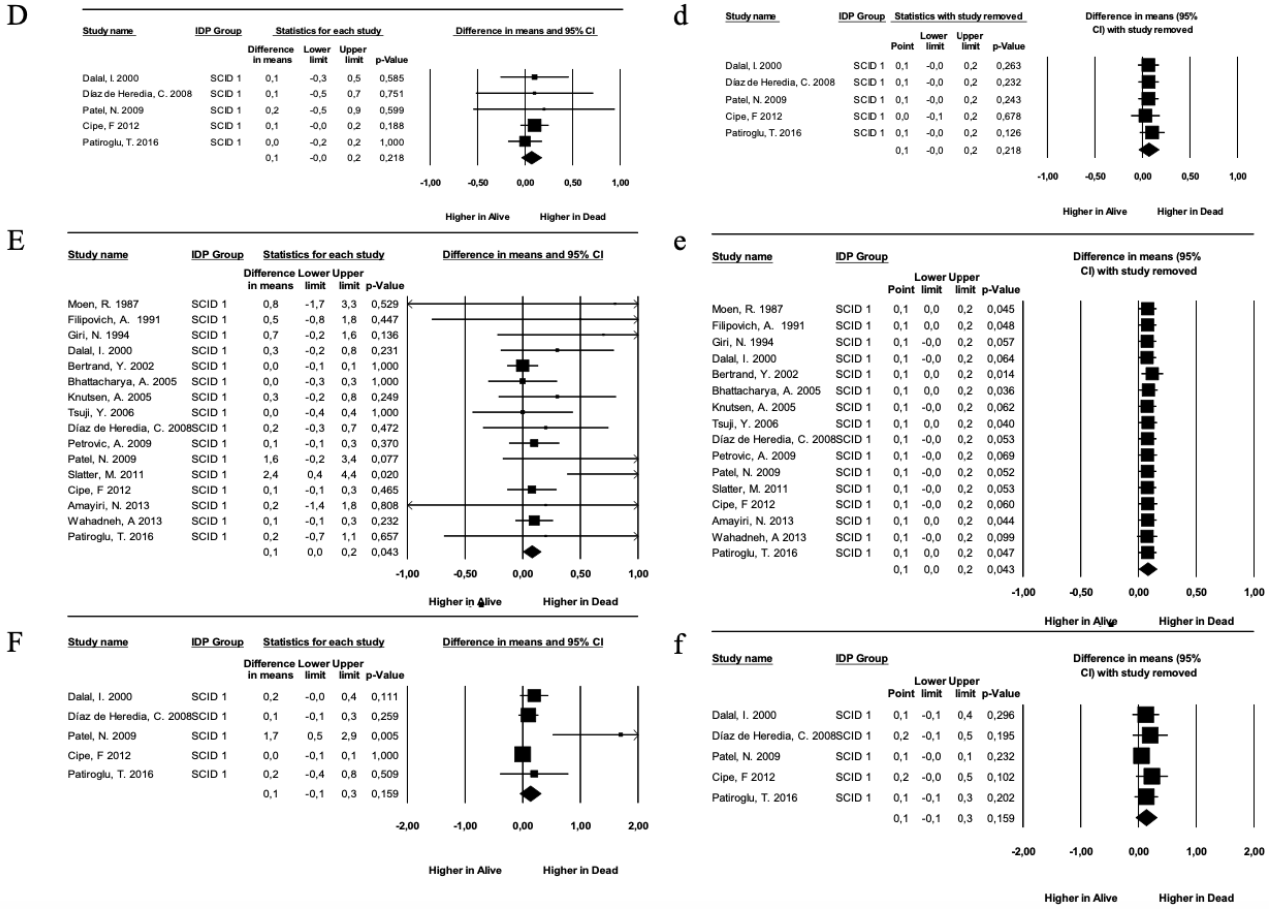


Figure 7. effects of age of diagnosis, age of treatment and time waiting for transplant on survival.

Discussion

HSCT remains as the only available treatment with curative potential for patients with PID. The arrival of new diagnostic techniques, as next generation sequencing, is exponentially increasing the number of PID diagnosed each year. It is difficult to know which patients should be treated with HCST, since the natural history and the results of HSCT in many PID are unknown. This systematic review evaluated the effectiveness of HSCT, from its first report in 1968 to the present, main indications as well as complications, and explored the effect of sex, donor compatibility and age of diagnosis and treatment on the results of effectiveness, by type of study.

A total of 5259 patients with PID undergoing HSCT were included. The methodological quality of studies was mostly good which makes the possibility that the results with less effectiveness come from suboptimal studies are unlikely. In addition, there was no evidence of publication bias for OS and EFS results. In 58% of the transplants were reported in the last decade, evidencing the increase and the validity of this procedure currently. In 43% of the patients were diagnosed with SCID1, which shows that this PID remains the main indication for HSCT within the PID group. For the first time, the detailed results of more than 3000

non-SCID patients are evaluated, this demonstrates the importance of this type of study in increasing statistical power by grouping large numbers of studies with a small sample size.

In 90% of patients were reported in descriptive cohort studies and description of national registries, which shows the importance of incorporating this type of registry to know the clinical results of patients with rare diseases. Given the nature of these diseases and that it is not considered ethical to carry out clinical trials on curative treatments, seven clinical studies were included, but their objectives were to evaluate efficacy of HSCT variations. In 66% of transplants were performed in Europe, reflecting whether the procedure is not performed to the same extent in the other regions or that the results from the rest of the world are not being published, especially from South América with only one article and seven patients from Brazil, and Africa where it was found only one article made in Egypt with 20 patients.

The case reports were the type of study with the highest number of publications. In rare diseases such as PID, this type of studies may be the only source of information available about adverse events and other particular conditions, which is why they are being used in systematic reviews recently (181–184). In this review, case reports were the source for extracting the main indications as well as complications related to HSCT in patients with PID. The main indication for deciding to do the transplant was the presence of infections, even before the genetic confirmation of the disease. This is important because normally patients who do not have a genetic diagnosis are not offered the possibility of a transplant (15). Nowadays expert advice is to take the HSCT decision based in the phenotype instead of the genotype (18). Regarding to complications, the main ones were the occurrence of infections and acute GVHD. These are the complications have been widely reported in transplanted patients in general (6,29). Especially, in patients with PID challenges of HSCT are even bigger. They are usually very young patients, given the susceptibility to infections, they can present active infections or even organ damage at the time of transplantation, the difficulty in finding compatible donors is greater because they frequently come from consanguineous families in which potential donors may be carriers of the disease or ethnic minorities that make it harder to find a potential donor (15,17).

Overall survival was 71% taking the 76 studies as unit of analysis or 67% using 188 subgroups of PID as unit of analysis. The difference is due to, when grouping patients into subgroups, if any of these were left with less than two patients, it was not considered for analysis. There was a significant difference in OS between the PID groups. The best survival results were for the groups of phagocyte deficiency, CID1, SCID 2, SCID1 and intrinsic defects, all with survival exceeding 62%, while the least favorable results were for diseases: CID2, antibodies deficiencies and dysregulation defects with the lowest survival being 46%. These differences have been observed previously and can be explained by the clinical characteristics and complications of each disease. Indeed, because of this heterogeneity, it has not been possible to establish a universal TCMH protocol so far for the treatment of PID (17). The recommendations of the EBMT / ESID guidelines, establish a diverse set of protocols depending on the type of PID and the availability or not of a compatible donor (23). These guidelines recommend that HSCT be performed only in centers with sufficient experience in the pre- and post-HRCT management of patients with PID to ensure favorable results. On the other hand, we did not find significant differences when comparing the results of OS among the continents of the study, which suggests that HSCT has comparable results independent of the place of execution, however, the majority of studies came from Europe,

Asia and North America; it is necessary that results of other regions be published to ensure that the effectiveness is comparable.

The overall survival results have improved markedly over time. In the meta-regression an improvement of 3% was found in each year with respect to the previous one. Before the year 2000 the OS was only 54% and in the last decade the combined results reach 74%. Recently published results have even reported survival in European centers that are close to 90% event in adults patients (17,18,185). The reasons for the improvement in the survival results can be among others, the increasingly early diagnosis of the patient which allows them to be referred to specialized centers, to the development of high-resolution HLA typing, use of alternative donors, new stem cell sources and availability of less toxic conditioning regimens (24).

The percentage of EFS was 59% regardless of the unit of analysis. The result was similar between PID groups, regions or year of publication. This is the percentage of patients who survived with a successful transplant, there was no graft rejection and therefore there was no need to practice a second transplant. This is very important because a second transplant increases the risks and doubles the already high costs of the procedure.

Recent narrative reviews also describe the results of effectiveness of HSCT in some of the main PID. Castagnoli *et al*, describes recent findings in SCID, MHCII, CD40L, DOCK8, DOCK2, WAS, CHH, HIGE, CGD, IPEX, STAT1, STAT3, LRBA, CTLA4 and XLP (24). Mitchell R, describes results of SCID, WAS, HLH, CVID, CD40L, among others. It also describes the long-term adverse effects (25). Gavrilova T, presented results for SCID, IPEX, CGD, WAS, and DOCK8 (186). And Slatter *et al*, describe results for SCID, WAS, CGD, DOCK8, CVID, IPEX, CTLA4, LRBA, PI3K, STAT1 (18). These reviews only describe the most recent findings and do not assess the cumulative effectiveness of any of the diseases.

In relation to the follow-up time, this was relatively short to assess all long-term effects of HSCT. 4.2 years for non-SCID patients and 3.3 years for SCID patients. Most deaths occur within the first post-transplant year and survival seems not to decrease over time, which points to some stability in the success of the transplant in the medium term and perhaps long term in these patients.

Interestingly, no differences were found in the proportion of 100% compatible donors between individuals who survived the transplant and those who did not. A higher degree of compatibility has been previously associated with better results in terms of survival and lower complications such as graft versus host disease (6,29). It is difficult to explain this result, probably the number of studies and patients in which compatibility was reported was not large enough to identify these differences. Possibly also the conditioning regime (data not extracted) changes according to degree of compatibility and has some mitigating effect on the final result, however, the conditioning regime has not previously been associated as a risk factor for survival (23). The source of the stem cells (peripheral blood, bone marrow or umbilical cord) and if the compatible donor is familiar or unrelated, have not been associated with better survival (17,23,29). However, access to donors is rapid in the case of related, haploidentical or cord blood unit compatible donors but delayed in the case of compatible unrelated donors, a factor that may affect survival (24).

On the other hand, it was demonstrated for the first time using meta-analysis that, at an earlier age of diagnosis and treatment, as well as shorter waiting time for treatment after being

diagnosed, are associated with better results of effectiveness for transplantation. Although not all comparisons achieved a statistically significant difference, the trend and clinical significance of findings are evident. In all studies, without exception, the punctual estimate of the mean age of diagnosis and transplantation was higher in deceased patients compared to patients who survived. In addition to this, it was also evident in all cases that the patients who died were waiting longer to receive the transplant after having the clinical diagnosis. These results are clear, even though some studies that reported significant differences according to age were not included in the comparison because they did not report individual age data per patient (15,28,187). These results could be explained by the fact that the older, the greater the risk of infections and organ damage at the time of transplantation. Indeed, the Gennery AR study suggests that the presence of infections at the time of transplantation is a risk factor for survival (15). The importance of early diagnosis had already been evidenced in the case of SCID (29,188,189), CGD (190), WAS (187), and CD40L (191). Patients with SCID are diagnosed and treated earlier and expect less time for transplantation compared to the non-SCID patient group. This is because in the first case the symptoms and severity of the disease appear earlier, and the genetic diagnosis is clearly established. In addition, in recent years, screening has been implemented for newborns that can be diagnosed at birth. In the case of a non-SCID patient, added to the fact that the appearance of the first symptoms may be later, the decision of when or not to do a HSCT is based on the characteristics of the disease and the evaluation of the individual condition of each patient, and this decision is difficult mainly in adults who have survived childhood and adolescence with prophylactic treatment. These results suggest that both the risk of HSCT and the evolution of the disease should be considered at the time of diagnosis and not wait for the appearance of major complications to make the decision to transplant.

Main limitations of this review are the low number of patients in some articles, short follow-up times that do not allow us to rule out long-term complications and verify long-term cure. In order to avoid selection bias, no search was made with the specific name of diseases and therefore those relevant publications that did not have the word primary immunodeficiency or their synonyms were not included. Ideally, systematic reviews should include only controlled clinical trials, but in these rare diseases it is extremely difficult to conduct these studies. However, we consider that the measurement of the outcome of whether or not the patient survived the procedure and age are not very likely to be influenced by the investigator nor should they be affected by the common biases of the observational studies.

The strengths of the study are, the completeness in the search, a fairly large number of patients were included, since it is a rare disease, more than 5000 patients is undoubtedly the largest compilation of results to date for PID. No limits were included for publications or language, year, or type of study, so all publications were captured from the first transplant to the present. Finally, the high heterogeneity found was explained by doing subgroup analyzes, sensitivity analyzes and meta-regression.

Conclusion

For the first time the effectiveness of HSCT in patients with PID worldwide was systematically evaluated. HSCT is an effective option for the correction of a wide variety of primary immunodeficiencies. There are still serious complications related to the transplant, however the effectiveness results have improved significantly over time. Long-term survival

has not been studied extensively but it seems that remission is complete and stable after having survived the first years. The age of the transplant plays a decisive role in the effectiveness of HSCT, the decision to proceed with the transplant should be taken by evaluating the risks and benefits as soon as possible after the phenotypic diagnosis, and not waiting for the occurrence of threatening complications for lifetime.

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