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ORIGINAL ARTICLE

Allogeneic Hematopoietic Stem Cell Transplantation Activity in Inborn Errors of Immunity in Russian Federation

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Abstract

Purpose Allogeneic hematopoietic stem cell transplantation (HSCT) is an established therapy for many inborn errors of immunity (IEI). The indications for HSCT have expanded over the last decade. The study aimed to collect and analyze the data on HSCT activity in IEI in Russia.

Methods The data were collected from the Russian Primary Immunodeficiency Registry and complemented with information from five Russian pediatric transplant centers. Patients diagnosed with IEI by the age of 18 years and who received allogeneic HSCT by the end of 2020 were included.

Results From 1997 to 2020, 454 patients with IEI received 514 allogeneic HSCT. The median number of HSCTs per year has risen from 3 in 1997–2009 to 60 in 2015-2020. The most common groups of IEI were immunodeficiency affecting cellular and humoral immunity (26%), combined immunodeficiency with associated/syndromic features (28%), phagocyte defects (21%), and diseases of immune dysregulation (17%). The distribution of IEI diagnosis has changed: before 2012, the majority (65%) had severe combined immunodeficiency (SCID) and hemophagocytic lymphohistiocytosis (HLH), and after 2012, only 24% had SCID and HLH. Of 513 HSCTs, 48.5% were performed from matched-unrelated, 36.5% from mismatched-related (MMRD), and 15% from matched-related donors. In 349 transplants T-cell depletion was used: 325 TCRαβ/CD19+ depletion, 39 post-transplant cyclophosphamide, and 27 other. The proportion of MMRD has risen over the recent years.

Conclusion The practice of HSCT in IEI has been changing in Russia. Expanding indications to HSCT and SCID newborn screening implementation may necessitate additional transplant beds for IEI in Russia.

Keywords Primary immunodeficiency · inborn errors of immunity · hematopoietic stem cell transplantation · transplantation activity

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Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is a widely used curative therapy for patients with inborn errors of immunity (IEI) (formerly known as primary immunodeficiency (PID)). The indications for HSCT have been vastly expanded over the last decade [1]. This is related to many factors, including improvements in HSCT technologies and pre- and peri-HSCT supportive care, which have led to better survival and decreased morbidity. Another important factor contributing to expansion of HSCT indication is accumulation of knowledge in IEI natural disease course and HSCT outcomes [2–4].

The European Blood and Marrow Transplantation (EBMT) report on HSCT trends in 2019 estimated that of 3123 allogeneic HSCTs performed in 121 pediatric centers from 27 countries, about 19% of indications accounted IEI [5]. The EBMT 2017 report on HSCTs in non-malignant disease demonstrated significant increase in HSCTs performed annually for IEI in Europe over the recent years [6].

National registries are also an important instrument to analyze changing practices in IEI care, including HSCT activity. Recent reports of the German and United Kingdom (UK) PID registries demonstrated a significant increase in IEI HSCTs [7, 8]. A recently published report of the Russian National PID Registry indicated HSCT performed in 342 Russian IEI patients by February 2020, although the data on HSCTs were incomplete due to underreporting [9].

We collected and analyzed the data on allogeneic HSCTs performed in pediatric IEI patients in Russia.

Methods

The primary data about allogeneic HSCT performed in IEI in Russia were collected from The Russian PID Registry of the National Association of Experts in PID (NAEPID), and due to detected HSCT underreporting, later complemented with information from all five Russian pediatric centers performing HSCT in non-malignant conditions. The study group included pediatric patients diagnosed with IEI by the age of 18 years and who received allogeneic HSCT by the end of 2020. The IEI diagnoses were established clinically according to the European Society for Immunodeficiency (ESID) criteria [10] and either confirmed or not confirmed with molecular genetic analysis.

The patients were divided into ten groups of IEI according to the classification of the International Union of Immunological Societies (IUIS) [11]. The IEI with congenital bone marrow (BM) failure were not included in the study, as these patients have been historically under the care of hematology specialists. Patients with features of IEI, but no laboratory or clinical signs characteristic for a particular IEI group, were attributed to an "undefined IEI" group. Patients with non-severe combined immunodeficiency (SCID) or Omenn syndrome clinical phenotype [12] but having hypomorphic mutations of SCID genes were attributed to the combined immunodeficiencies (CID) less profound than SCID.

Sanger sequencing or next generation sequencing (NGS) in a targeted panel of IEI genes, or clinical exome, or whole exome was used for molecular genetic testing in most of the patients.

The registry analysis included patients diagnosed with IEI under the age of 18 by the end of 2020, excluding selective IgA deficiency, transient hypogammaglobulinemia of infancy, "periodic fever, aphthous stomatitis, pharyngitis, adenitis" (PFAPA) syndrome, chronic recurrent multifocal osteomyelitis, and IgG4-related disease. The registry data collection was censored in March 2022.

For HLA-typing, in all donors and patients, polymerase chain reaction was used, with low and high resolution techniques before and from 2022, respectively. As determined previously for unrelated donors [13], 10/10, 9/10 and 8/10 donor-recipient HLA-match was defined as "matched unrelated donor" (MUD).

The HSCT data collection was performed in January 2022 and analyzed in September 2022 with XLSTAT 2022 software (Addinsoft, France). The patients were censored at the time of death or last follow-up in survivors. The Kaplan-Meier method was used to estimate the probability of overall survival (OS) with 95% confidence intervals (*CI*).

Results

Number of Annual HSCT

From 1997 to 2020, 454 patients with IEI received 514 allogeneic HSCTs in 5 Russian centers: 398 received one, 52 two, and 4 three transplants. The number of annually performed HSCTs has greatly risen over the last 10 years (Fig. 1). The median number of HSCTs per year was 3 in 1997–2009, 15 in 2010–2014, and 60 in 2015–2020. Over the last 10 years, second transplant procedures accounted for 8 to 20% of all performed HSCTs. The distribution of HSCTs between the transplant centers is shown in Fig. S1 supplement.

Distribution of Diagnosis

According to the IUIS classification, 442 patients were divided into 8 groups of IEI (excluding BM failures; and

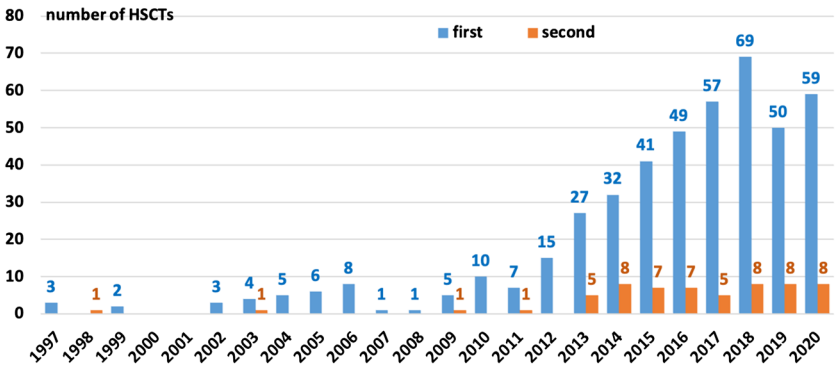

Fig. 1 Annual number of first and second HSCTs in IEI. *The bar chart represents distribution of numbers of first and second HCSTs performed in Russia between the years from 1997 to 2020*

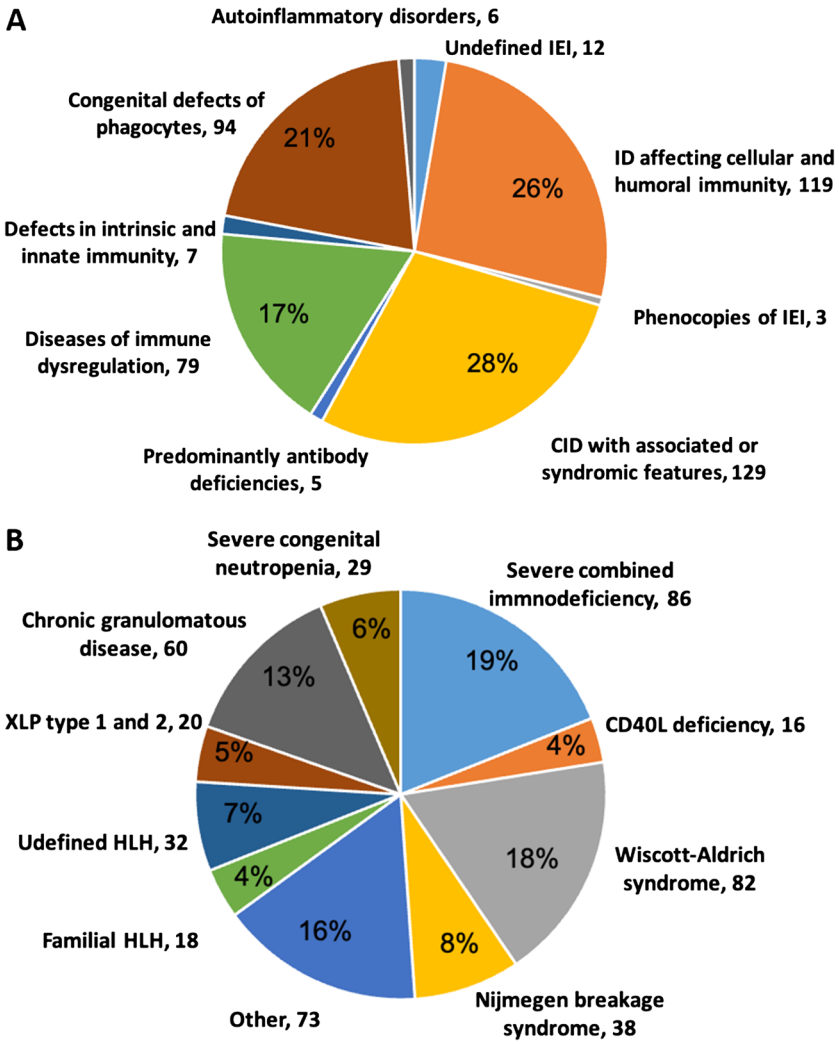

Fig. 2 Distribution of patients by IEI diagnoses by groups and diseases. *The pie chart represents distribution of IEI diagnoses (**A**) and disease (**B**). HLH, hemophagocytic lymphohistiocytosis; XLP 1 and 2, X-linked lymphoprolypherative disease type 1 and 2; IEI, inborn error of immunity; CID, combined immunodeficiency; ID, immunodeficiency*

none had complement deficiencies), and 12 patients were attributed to undefined IEI group (Fig. 2A). The most common diagnoses are shown in Fig. 2B. The most common groups of IEI were immunodeficiency affecting cellular and humoral immunity (26%), CID with associated or syndromic features (28%), phagocyte defects (21%), and and diseases of immune dysregulation (17%). Of 119 patients with cellular and humoral defects, 86 (72%) had SCID and 33 (28%) CID, which is less profound than SCID. Of 129 patients with syndromic CID, the majority had Wiscott-Aldrich syndrome (WAS) (64%), and Nijmegen breakage syndrome (NBS) (31%). Of 94 patients with phagocyte disorders, 64% had chronic granulomatous disease (CGD) and 30% congenital neutropenia. Of 79 patients

with immune dysregulations, 55% had hemophagocytic lymphohistiocytosis (HLH), 23% X-linked lymphoproliferative (XLP) disease type 1 and 2, and 22% other diseases. The distribution of IEI diagnosis as indication to HSCT has changed over the years: before 2012, the majority (65%) of patients had SCID and HLH, and after 2012, SCID and HLH accounted only 24% of the patients receiving HSCT (Fig. 3A).

In 370 (81%) patients, molecular defects in IEI causative genes have been confirmed: 284 by Sanger sequencing, 75 by NGS of IEI genes, 6 whole exome, and 5 clinical exome. In 329 of 370 (89%) patients, molecular defects were found before HSCT and in 41 (11%) patients after HSCT. In 41 patients who received a molecular diagnosis after HSCT, 26 had SCID and 15 other IEI. Before 2012, the molecular defect was known at HSCT in 17 of 57 (33%) of the patients and after 2012 in 311 of 399 (78%) of the patients.

Age Distribution

The median age at IEI diagnosis was 1 year (range 0–17.9); the median age at first HSCT was 2.3 years (range 0.12–19.6); male/female ratio was 3:1. The median time between IEI diagnosis and HSCT was 1.8 months (range 0.3–10.8) in SCID and 12.9 months (range 0.95–197) in other IEI, and in 1 patient with LIG4 deficiency, the IEI diagnosis was made after the HSCT was performed for severe aplastic anemia. The median age at IEI diagnosis and HSCT in different groups of IEI is shown in Table 1.

All patients were allocated into one of the 5 age groups at the time of HSCT. The distribution of patients between the age groups is shown in Fig. 3B. The most frequent indication for HSCT before 1 year of age was SCID (70%), from 1 to 3 years WAS (30%), from 3 to 7 years CGD (25%), and from 7 to 12 years NBS (20%).

HSCT Details

The data on transplant details were not available for one patient. Of 513 HSCTs, 249 (48.5%) were performed from MUD (182 — 10/10, 63 — 9/10, and 4 — 8/10 HLA-matched), 76 (15%) from matched-related donor (MRD) (≥ 9/10 HLA-matched), and 188 (36.5%) from mismatched-related donor (MMRD) (≤ 8/10 HLA-matched); in 12 of 56 second HSCTs, the same donor as for the first HSCT was used. The preferred donor type has changed over the last 10 years with an increased proportion of MMRD and predominance of related donors used in 2020 (a year of COVID-19 pandemic) (Fig. 4). The

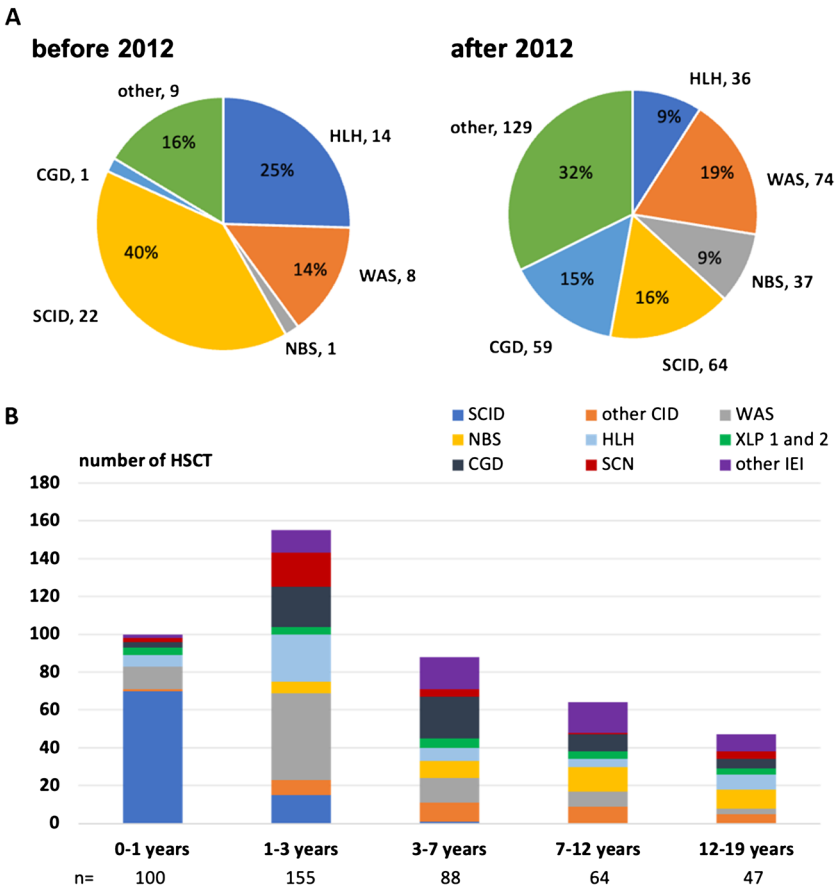

Fig. 3 Distribution of IEI diagnoses before and after 2012 and between the age groups at HSCT. *The pie chart represents distribution of IEI diagnoses before and after 2012 (**A**). The bar chart represents distribution of IEI diagnoses between the age groups at HSCT (**B**). CGD, chronic granulomatous disease; SCID, severe combined immunodeficiency; WAS, Wiscott-Aldrich syndrome; NBS, Nijmegen breakage syndrome; HLH, hemophagocytic lymphohistiocytosis; SCN, severe congenital neutropenia; XLP 1 and 2, X-linked lymphoproliferative disease type 1 and 2; IEI, inborn error of immunity; other CID, other than SCID combined immunodeficiency*

Table 1 Number of registry patients diagnosed with IEI in Russia and patients received allogeneic HSCT

IEI group	IEI disease	Number of diagnosed IEI			Number (percentage) of received HSCT			Median (range) age**	
		Total	Before 2012	2012-2020	Total	Before 2012	2012-2020	at IEI diagnosis, years	at HSCT, years
All		2775*	691	2084	482* (17%)	59 (9%)	417 (20%)	1 (0-17.9)	2.3 (0.1-19.6)
ID affecting cellular and humoral immunity	all	290	72	218	124 (43%)	25 (35%)	99 (45%)	0.6 (0,1-17.3)	0.9 (0.1-17.6)
	SCID	146	47	99	90 (62%)	23 (49%)	67 (68%)	0.5 (0.1-2.8)	0.7 (0.1-3.2)
	other CID	144	25	119	34 (24%)	2 (8%)	32 (27%)	3 (0.2-17.3)	6.1 (0.7-17.7)
CID with associated or syndromic features	all	743	187	556	141* (19%)	12 (6%)	129 (23%)	1.1 (0-17.1)	2.5 (0.2-17.7)
	WAS	166	64	102	92* (55%)	11 (17%)	81 (79%)	0.7 (0-11.7)	2 (0.2-12.9)
	NBS	97	30	67	38 (39%)	1 (3%)	37 (55%)	4.5 (0.2-16.8)	7.4 (1-17.2)
Predominantly antibody deficiencies		447	195	252	5 (1%)	-	5 (2%)	4.6 (0.7-13)	10.4 (5.3-14.4)
Diseases of immune dysregulation	all	255	70	185	80 (31%)	16 (23%)	64 (35%)	2.1 (0-15.2)	2.6 (0.4-18.1)
	HLH	64	18	46	50 (78%)	14 (78%)	36 (78%)	1.6 (0-15.2)	2.3 (0.4-18.1)
	XLP 1-2	37	8	29	21 (57%)	2 (25%)	19 (66%)	4.1 (0.1-12.0)	5.2 (0.5-17.5)
Congenital defects of phagocyte	all	299	85	214	104 (35%)	4 (5%)	100 (47%)	1.2 (0-17.9)	3.1 (0.6-19.6)
	CGD	146	46	100	70 (48%)	1 (2%)	69 (69%)	1.8 (0.2-17.4)	3.6 (0.6-19.6)
	SCN	138	39	99	28 (20%)	3 (8%)	25 (25%)	0.7 (0-15.5)	1.8 (1-17)
Defects in intrinsic and innate immunity		52	8	44	7 (13%)	-	7 (16%)	0.8 (0.1-10)	3.7 (0.4-11.4)
Autoinflammatory disorders		283	16	267	6 (2%)	-	6 (2%)	2.9 (0.9-11.5)	7.2 (1.5-12.0)
Complement deficiencies		137	26	111	-	-	-	-	-
Phenocopies of IEI		12	2	10	3 (25%)	-	3 (30%)	4.8 (0.8-5.5)	7.8 (3.5-8.1)
Undefined IEI		257	30	227	12 (5%)	1 (3%)	11 (5%)	4.2 (0.4-14.6)	5.2 (1.1-17.7)

*patients with WAS received gene therapy (2 before 2012 and 2 after 2012)

**in patients transplanted in Russia only

ID immunodeficiency, *CGD* chronic granulomatous disease, *SCID* severe combined immunodeficiency, *WAS* Wiscott-Aldrich syndrome, *NBS* Nijmegen breakage syndrome, *HLH* hemophagocytic lymphohistiocytosis, *SCN* severe congenital neutropenia, *XLP 1 and 2* X-linked lymphoprolypherative disease type 1 and 2, *IEI* inborn error of immunity, other *CID* other than *SCID* combined immunodeficiency

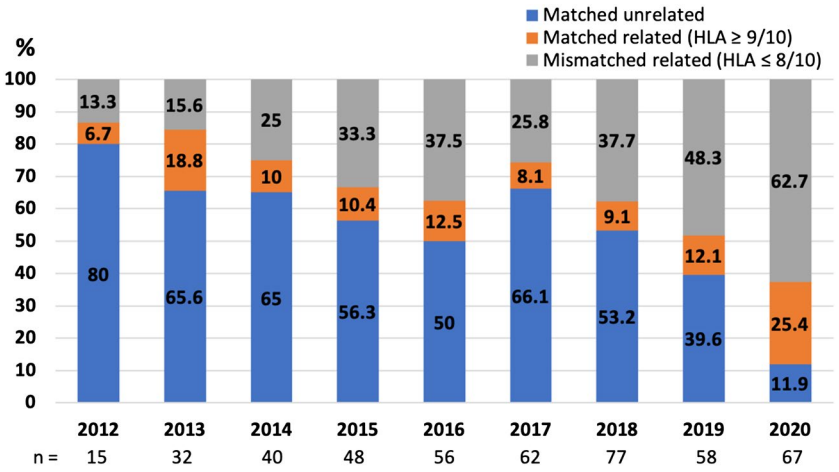

Fig. 4 Distribution of donor type used over the last 10 years. *The bar chart represents distribution of types of donors used for HSCT: matched unrelated, matched related, and mismatched related between years from 2012 to 2020*

graft source in 383 patients was peripheral blood stem cells (PBSC), in 121 patients BM, in 7 patients umbilical cord blood (UCB), and in 2 a mixture of BM with PBSC or UCB. In 349 various methods of T-cell depletion were used: 325 TCRαβ/CD19+ depletion, 39 post-transplant cyclophosphamide (Pt-Cy), 24 CD34+ selection, 2 in vitro Campath, and 1 TCRαβ/CD19+ depletion in combination with Pt-Cy. T-cell depletion methods were used not only for grafts from MMRD, but also in 188 of 249 (75%) MUD and in 17 of 76 MRD (22%).

Survival and Mortality

The median follow-up time in 338 survivors in January 2022 ($n = 338$) was 4.4 years (range 1–24.5). The median follow-up time of death was 0.33 years after HSCT (range 0.01–4.1). OS in 454 patients was 0.74 (95% *CI* 0.69–0.78). OS significantly varied between SCID and other IEI: 0.56 (95% *CI* 0.46–0.67) versus 0.78 (95% *CI* 0.73–0.82), respectively, $p < 0.0001$. OS has significantly improved over the years; before 2012 in 55 patients, it was 0.54 (95% *CI* 0.41–0.68) and after 2012, in 399 patients 0.76 (95% *CI* 0.72–0.8), $p < 0.0001$; with the median follow-up time of 12.4 (range 2.1–24.4) and 4.1 (range 1–10) years, respectively. The OS in patients with active disease complications at HSCT (infectious, autoimmune/autoinflammatory, or malignant) ($n = 262$) was 0.65 (95% *CI* 0.58–0.7) versus 0.86 (95% *CI* 0.81–0.91) in patients without complications ($n = 192$), $p < 0.0001$. The causes of death in 107 patients were transplant-related; in 8 patients, they were related to prior disease/malignancy relapse or progression, or secondary malignancies, and not available for 1 patient.

HSCT Coverage of Registered Patients

The registry analysis included 2775 pediatric patients with IEI diagnosed by the end of 2020. Allogeneic HSCT or gene therapy was performed in 482 of 2775 (17%) patients; 478 received HSCT and 4 with WAS gene therapy. All 4 WAS patients received gene therapy, and 24 patients received allogeneic HSCT abroad. The percentage of registry patients receiving HSCT in different groups of IEI is shown in Table 1. Despite a significantly increased number of patients diagnosed with IEI after 2012, only 9% of patients with IEI received HSCT before 2012, whilst about 20% of patients diagnosed with IEI received HSCT after 2012. After 2012, the percentage of registered patients with IEI receiving HSCT remained the same for HLH (78%), slightly increased for SCID (from 49 to 68%) and dramatically (more than 2 times) increased for many other diseases — WAS, CGD, SCN, NBS, XLP 1 and 2, and others.

Discussion

Indications for HSCT in IEI have been expanding over the last decade. The most detailed report on IEI HSCT in Europe was published by Gennery et al. in 2010, which demonstrated improved survival for both SCID and non-SCID diseases (less than 80 and 70%, respectively) [14]. Since that report, no large multicenter analyses of HSCT outcomes for IEI were performed in Europe; however, many recent studies report changing transplant practices and improved HSCT outcomes with OS ranging from 86 to 89% for specific IEI, such as CGD, WAS, XLP 1 and 2, and many others [3, 15, 16]. Importantly, there is an increasing number of novel indications to HSCT, both from recently described IEI or reconsidered policies for well-known IEI [17–19].

The first HSCT for IEI in Russia was performed in 1997 in patients with HLH, and the landscape of IEI patients receiving HSCT has changed since then. Corresponding to the European multicenter data [14], before 2012, the main indication to HSCT in our group was SCID (40% of transplants), while after 2012 SCID accounted only 16% of transplants, and more HSCTs are performed in such diseases as CGD, NBS and other IEI.

The proportion of patients from different groups of IEI receiving HSCT in Russia is similar to that reported by the German PID registry [7]. Remarkably, in our group, the patients with distinct diseases predominantly received HSCT at specific age intervals, which is mostly related to the typical time of disease presentation and diagnosis. Apart from SCID, where HSCT has always designated as an emergency life-saving procedure, quite a short time between IEI diagnosis and HSCT is seen for the patients with definite indications for HSCT and high risks of life-threatening complications, such as HLH, WAS, or SCN. A longer interval between IEI diagnosis and HSCT is seen in groups of patients, where historically HSCT was not a routine option, and patients have been considered for HSCT after they developed serious complications, such as NBS or hypomorphic SCID.

The OS in IEI after HSCT varies between countries; recent reports demonstrate lower rates of survival in low-income countries and higher rates in high-income countries. Thus, the reported OS is 0.61 in India [20], 0.63 in Colombia [21], 0.71 in Brazil [22], 0.67–0.74 in Japan, [23, 24], 0.83 in the UK [8], and least 0.92 Germany [7]. In Russia, the OS in all IEI patients who received HSCT is 0.74, and since 2012, the OS has improved from 0.54 to 0.76.

A lower survival than in European countries may be related to delayed IEI diagnosis in Russia [9], which leads to uncontrolled disease complications seen in many patients at HSCT. Moreover, the biggest Russian centers performing HSCT in IEI do not select patients eligible for HSCT (apart from those having life-threatening conditions and requiring intensive care). In our study, HSCT with uncontrolled disease complications lowered the survival to 0.65 from 0.86 in the patients without complications.

The most significant decrease in OS in Russia is seen for SCID — 0.54. This is mainly related to absent newborn screening and late SCID diagnosis. The median age at SCID diagnosis in our group is 6 months and most of the patients at diagnosis and HSCT are infected with various pathogens [25, 26]. Implementation of newborn screening for SCID may improve survival in these patients, but however, it will

require at least about 15 more HSCTs performed annually (according to approximate SCID incidence of 1 per 58,000 newborns estimated in the USA [27]).

The number of annual HSCTs performed in Russia for IEI started to increase from 2012, while similar trends were observed rather earlier (from 2008 to 2010) in Germany and the UK [7, 8]. This may be related to a few factors. Firstly, the leading center for pediatric immunology and IEI HSCT in Russia, where most of the patients with IEI have been diagnosed and transplanted, was opened in 2012. This was later accompanied by implementation into routine practice of new generation sequencing technology allowing better diagnosis of IEI [9], and improvements in IEI pre-HSCT care and HSCT practices, allowing better survival for IEI. Thus, the number of patients with a known genetic defect at HSCT in Russia increased from 33 to 78% after 2012.

Importantly, despite an overall shortage of HSCT activity in Russia [28], the proportion of patients in Russian IEI registry receiving HSCT or gene therapy is 17% and is similar to the UK and the Netherlands data [8, 29]. Certainly, this comparison is limited by expected underreporting of IEI by the Russian registry [9] and purely pediatric patients included in the current analysis, whilst other registry data included adults. For many years, HSCT in adult patients has not been a common practice for IEI, although this practice has been changing and HSCT became a treatment option for adult patients with IEI [30]. Unfortunately, HSCT is still limited for adult patients with IEI in Russia. Also, more patients in the UK received gene therapy, but access to this therapy is limited for Russian patients.

The use of MMRD for IEI in Russia has risen remarkably since 2012. This was made possible due to the implementation TCRαβ/CD19+ depletion technology used in Russia for HSCT in IEI since 2012 and Pt-Cy used from 2014. Both methods have demonstrated efficacy in IEI HSCT [13, 31–33]. Importantly, this allowed the HSCT programme for IEI to continue during the COVID-19 pandemic in 2020, when access to MUD was seriously affected. Of note, the number of second HSCT procedures in Russia remains consistent (about 13% of all HSCTs). This corresponds to a rejection rate in IEI patients reported for IEI by one of the participating centers [34].

The current study is limited by its retrospective character and variety of HSCT approaches used in different centers for different conditions, which precludes analysis of transplant practices influencing survival. However, the study helped to estimate a level of IEI patients receiving that type of therapy in Russia to approximate the number of additional beds required since the implementation of newborn screening for SCID (which is planned for 2023). Reconsideration/development of educational programs for pediatricians and related specialists to improve IEI diagnosis in Russia may lead to increased post-HSCT survival. Introduction of immunology practices into adult HSCT may help develop adult IEI HSCT service.

To conclude, HSCT is an emerging therapy for many IEI, and the practice of HSCT in IEI has been changing. National IEI registries are an important instrument for monitoring the main trends in IEI care including HSCT. Improved IEI diagnosis may result in increased post-HSCT survival. Expanding indications for HSCT in IEI and implementation of SCID newborn screening will necessitate additional transplant beds for IEI in Russia.

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Authors' Contribution AL collected, analyzed and interpreted the data and prepared the manuscript. AM contributed to the data collection. EM, OP, TB, LV, GB, and YS provided the data. ES, IK, LF, AS, LZ, and DB led the immunology services and/or IEI HSCT programs in transplant centers. AR conducted the study. All the authors read and approved the final manuscript.

Data Availability The dataset used during the current study is available from the corresponding author on reasonable request.

Declarations

Ethics Approval This is a retrospective data analysis. No ethical approval is required.

Consent to Participate Institutional consent forms for data collection and sharing were obtained from all the patients or their legal guardians.

Consent for Publication Not required, as no individual person's data are demonstrated.

Competing Interests The authors declare no competing interests.

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