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Continuous and differential improvement in worldwide access to hematopoietic cell transplantation: activity has doubled in a decade with a notable increase in unrelated and non-identical related donors

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Short title:
Worldwide improvement in the access of HCT

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Contributions

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Data Sharing Statement:

The data of this study are not publicly available. The Global Activity Data of the WBMT are managed in accordance with WBMT Research Guideline.

Abstract

Promoting access to and excellence in hematopoietic cell transplantation (HCT) by collecting and disseminating data on global HCT activities is one of the principal activities of the Worldwide Network for Blood and Marrow Transplantation, a non-Governmental organization in working relations with the World Health Organization. HCT activities are recorded annually by member societies, national registries and individual centers including indication, donor type (allogeneic/autologous), donor match and stem cell source (bone marrow/peripheral blood stem cells/cord blood). In 2018, 1,768 HCT teams in 89 countries (six WHO regions) reported 93,105 (48,680 autologous and 44,425 allogeneic) HCT. Major indications were plasma cell disorders and lymphoma for autologous, and acute leukemias and MDS/MPN for allogeneic HCT. HCT number increased from 48,709 in 2007. Notable increases were seen for autoimmune diseases in autologous and hemoglobinopathies in allogeneic HCT. The number of allogeneic HCT more than doubled with significant changes in donor match. While HCT from HLA identical siblings has seen only limited growth, HCT from non-identical related donors showed significant increase worldwide. Strongest correlation between economic growth indicator of gross national income/capita and HCT activity/ten million population was observed for autologous HCT (r=0.79). HCT from unrelated donors showed strong correlation (r=0.68), but only moderate correlation (r=0.51) was detected from related donors. The use of HCT doubled in about a decade worldwide at different speed and with significant changes regarding donor match as a sign of improved access to HCT worldwide. Although narrowing, significant gaps remain between developing and non-developing countries.

INTRODUCTION

After more than 65 years from the first attempt, hematopoietic cell transplantation (HCT) remains the only curative treatment for many malignant and non-malignant hematologic disorders(1). Destruction of malignant cells by intensive preparative regimens, the replacement of a diseased hematopoietic system and the induction of immunological reactions against tumor cells are key mechanisms for the curative success of allogeneic HCT. Autologous HCT was first reported in the 1980s and used to facilitate maximal chemo/radiotherapy dosing and to restore the hematopoietic system. Recently, autologous HCT has also been used to correct genetic aberrations with gene modified/edited hematopoietic stem cells. (2)

Newer developments have extended HCT to elderly or frail patients with the introduction of reduced or non-myeloablative preparative regimens and to patients lacking a matched donor with the use of mismatched related donors and cyclophosphamide post-transplant. Since the beginning of the new millennium, improvements in supportive care have in addition reduced morbidity and mortality.(3-5) The lack of alternative curative treatments contributed to the continuous increase and diffusion of HCT worldwide reaching 1.5 million procedures since 1957. (6-8) However, despite its increasing application and ease of access, HCT continues to be a highly specialized and expensive treatment, that requires extensive experience, significant infrastructure and a multidisciplinary team of specialists.

Increasing specialization and complexity of health care systems still threaten the equity of access to global HCT. Having declared the transplantation of organs, cells and tissues a global priority, the World Health Organization (WHO; www.who.org) formed a task force to evaluate continuously equity of access, quality, safety and evolving trends. The Worldwide Network for Blood and Marrow Transplantation (WBMT; www.wbmt.org), a non-governmental organization (NGO) in working relation with the WHO, was established with the mission to support excellence in HCT worldwide. Regular activity reporting is of fundamental importance in a quality management system and one of the major tasks of the WBMT. (6-8) Up-to-date

information on indications, use of different technologies, donor types and trends over time will provide the basis for computing worldwide HCT utilization in different diseases (and indirect information on non-HCT treatments) as previously described for multiple myeloma (MM) and acute myeloid leukemia (AML).(9, 10) The global activity surveys help support physicians to provide patient counselling and guide health care agencies' to build the required infrastructure plans. Informed by the surveys, WBMT aims at narrowing the gaps by conducting workshops to promote and support the development of new HCT programs, and to optimize existing programs.(11, 12) Sharing accumulated experiences, successes and setbacks continue to be a cornerstone for improving access and outcomes of HCT.

Biennial reports were published by the WBMT from 2006 on. Up to 2016, a major but differential activity increase was described across all regions, higher in developing as compared to developed countries. Despite narrowing, gaps remained especially in the Africa and Eastern Mediterranean region. With this survey, we would like to report the developments up to the year 2018 and discuss opportunities to improve the access to HCT further.

METHODS

Study design

This retrospective observational study involved the worldwide HCT activity from the first published series of bone marrow transplants collected from the scientific literature and from member societies for very early transplants. After 2006, activities were obtained annually through the WBMT network using a unified center-based reporting system. Since 2007, reports on HCT activity from all WHO regions are being continued. The total number of HCT available in the registry were computed summing up the reports from 2006 to 2018. HCT activity analysis by WHO regions are performed comparing 2018 to 2007. Details of data collection and validation is described in Supplemental Method.

Main outcome measures were the spread of HCT over time and transplants by donor type, country of origin, and WHO region. Secondary outcome measures were to document any trends in the number of HCT by donor type or region, to classify these trends, and quantify differences in the use of autologous or allogeneic HCT across indications and regions. Population data and economy and growth indicator data were obtained from the World Bank (https://databank.worldbank.org/home.aspx).

As no individual patient data were used no ethics committee approval was mandated.

Participating HCT teams, groups, countries and continents

In 2018, 1,768 HCT teams in 89 countries over six WHO continental regions delivered HCT services globally [(www.who.int/about/regions/en/). These regions included the Americas (AMR; WHO regions North-, Middle- and South- America and Canada); Asia (SEAR/WPR; WHO regions South East Asia and Western Pacific Region, which includes Australia and New Zealand); Europe (EUR; which includes Turkey and Israel) and AFR/EMR (WHO regions Africa and Eastern Mediterranean)]. In this paper, AMR activities were divided in North America of US and Canada (AMR North) and Middle- and South- America (AMR Latin). European data were derived from the European Society for Blood and Marrow Transplantation (EBMT) database for the years 1965–89 and from the EBMT annual activity survey office since 1990. Non-European data were initially provided by the Center for International Blood and Marrow Transplant Research (CIBMTR) since 1964. They were supplemented or replaced by the activity surveys of the Asian Pacific Blood and Marrow Transplantation Group (APBMT) since 1974, the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR) since 1982, the Eastern Mediterranean Blood and Marrow Transplantation Group (EMBMT) since 1984, the Cell Therapy Transplant Canada (CTTC) since 2002, the Latin American Bone Marrow Transplantation Group (LABMT) since 2009, and the African Blood and Marrow Transplant Group (AFBMT) since 2010. Unrelated donor

and cord blood information were derived from the World Marrow Donor Association (WMDA) and Bone Marrow Donors Worldwide (BMDW).

Definitions

The number of patients who received a first HCT in the survey year is defined as the number of HCT in the corresponding year. Transplant rates (TRs) were computed as the number of HCT per 10 million inhabitants for each country not corrected for population age, without adjusting for patients receiving their HCT in a foreign country. We assessed patients by donor type (allogeneic or autologous), donor match, relation with patient (related or unrelated), stem cell source (bone marrow, peripheral blood stem cells, or cord blood) and indication including stage of the disease (according to https://www.ebmt.org/ebmt/documents/dismclfd-list-disease-classifications). There was no adjustment for patients who crossed borders and received their HCT in a foreign country. We computed Team Density (TD) for each country as the number of teams per 10 million inhabitants. Gross national income (GNI) per capita is a statistical measure that quantifies the average income earned by individuals in a country. Other definitions for macroeconomic indicators are described in Supplemental Method. Family member donors were categorized in two donor types as HLA-identical sibling (twin included in the HLA-id sibling donor group) or other relatives, which comprises haploidentical related donors.

RESULTS

Worldwide HCT activity in 2018

A total of 93,105 HCT were performed worldwide in 2018, including 48,680 autologous and 44,425 allogeneic transplants (Table 1). By region, the number of autologous HCT were largest in EUR, followed by AMR North, SEAR/WPR, AMR Latin, and EMR/AFR, while the

number of allogeneic HCT were largest in EUR, followed by SEAR/WPR, AMR North, AMR Latin, and EMR/AFR. Plasma cell disorders was the leading indication for autologous HCT in 2018 with approximately 1.6 times the number of autologous HCT for lymphoma, the second leading indication. Leading indications for autologous HCT are in all regions plasma cell disorders followed by lymphoma and solid tumors. In non-malignant indication, autoimmune disease is the most frequent indication for autologous HCT with especially high activity in Europe (n=546) and AMR Latin (n=159). After inclusion of the activities in 2017 and 2018, the WBMT registry comprises 877,883 (allo 408,611; auto 469,272) reports.

AML was the leading indication in allogeneic HCT. Leukemia [AML, acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), myelodysplastic syndromes (MDS)/myeloproliferative neoplasms (MPN), chronic lymphocytic leukemia (CLL), other leukemia] accounted for 75% of all allogenic HCT. Allogeneic HCT for nonmalignant diseases were performed in 7,186 patients (16% of allogeneic HCT) with bone marrow failure (n=3,276), hemoglobinopathies (n=1,827) and primary immune deficiencies (n=1,226) as the most prominent indications (Table 1).

Transplant rates (TR) in 2018

In order to account for population size of a country, TR, the number of HCT per 10 million inhabitants for each country, were calculated and presented in Figure 1 according to HLA-identical related, HLA-non-identical related and unrelated donors. The number of countries with TR of more than 25 for HLA identical sibling HCT, HCT from HLA mismatched related donors, HCT from unrelated donors, and unrelated CBT were 45, 26, 37, and 2, respectively, and the number of countries with TR of more than 50 were 25, 8, 33, and 1, respectively. As shown in Figure 1A TR for HCT from HLA-identical siblings amounted >51 HCT/10 million inhabitants in United States, central and western Europe, Saudi Arabia, Jordan, Lebanon, Turkey, Singapore, Hong Kong China, South Korea and Australia/New

Zeeland and were lowest in the majority of African countries and Ukraine. HCT from non-HLA-identical related donors were highest (>51 TR) in United States, Spain, France, Italy, Belgium, Lebanon, Singapore and South Korea. (Figure 1B) High density TR for HCT from unrelated donors (>101 TR) is concentrated in countries in Europe, North America, East Asia, and Australia. (Figure 1C) The TR from cord blood was highest in Japan. (Figure 1D)

Macroeconomic factors and HCT activity in 2018

Macroeconomics are important determinant for HCT activities, but not for all transplant types. Strongest positive correlation between GNI per capita and HCT activity in 2018 per 10 million population was observed for autologous HCT (correlation coefficient [r]=0.79, $p<0.001$). Overall allogeneic HCT showed less strong positive correlation ($r=0.66$, $p<0.001$) with GNI per capita. Among allogeneic, HCT from unrelated donors showed strong positive correlation ($r=0.68$, $p<0.001$). Moderate correlation was observed for both HCT from HLA-identical sibling donors and HCT from other related donors ($r=0.48$, $p<0.001$ and $r=0.45$, $p<0.001$, respectively; Figure 2) Three countries with GNI per capita >US$20,000 did not report any activity of allogeneic HCT (Cyprus, Iceland, and Luxembourg). Among the health expenditure macroeconomic indicators, per capita total expenditure on health on autologous HCT ($r=0.80$, $p<0.001$) and allogeneic HCT from unrelated donors ($r=0.70$, $p<0.001$) showed strong positive correlations. Other heath expenditure indicators expressed as percentages of total government expenditure, GDP, or total expenditure on health showed moderate to weak correlations (Table 3).

Global trends

Despite having a higher increase of allogeneic HCT since 2007, autologous HCT remains overall the most frequent HCT. HCT increase was mainly due to increase of yearly activity per HCT team reaching 52.7 in contrast to 35.1 in 2007 (Supplemental Figure 1). Team density

(TD; teams / 10 million inhabitants) of the 68 countries reported in 2007 was 4.92 (median, 25th and 75th percentile, 0.94 and 9.58) and 5.02 (median, 25th and 75th percentile, 1.86 and 9.30) in 2018. Reporting countries increased by 20 to 88 countries in 2018. Supplemental Figure 1 displays the number of HCT per 10 million population on the same scale for 2007 and 2018, showing increasing trend in the number of HCT per population for all, autologous, allogeneic, related, and unrelated HCT in all WHO regions.

Trends by region

Allogeneic HCT from HLA identical siblings has seen limited growth from 2007 to 2018, with the exception of SEAR/WPR, which has nearly doubled in number (Figure 3A). In AMR North, allogeneic HCT from HLA identical siblings has shown a subtle decline in most recent years. HCT from other related donors showed significant increase from 2007 to 2018 in all regions (Figure 3B). Instead, the global trend of unrelated cord blood transplantation showed decrease since 2011 in all regions except SEAR/WPR (Figure 3D). Thus, trends in the proportions of HCT from HLA mismatched related donors, from unrelated donors, and unrelated cord blood transplantation varied widely by region. EUR, AMR North and SEAR/WPR showed increasing trends in other related and unrelated donors and, with exception of SEAR/WPR, decreasing trends in cord blood transplantation. SEAR/WPR increased in all type of transplant (related, other related, unrelated cord blood) from 2007 to 2018 (Figure 3A, 3B, 3C and 3D). AMR Latin and EMR/AFR increased the activity primarily due to higher number of HCT from HLA mismatched related and unrelated donors.

Trends by indications

The number of autologous HCT for plasma cell disorders and lymphoma were similar in 2006 (Table 1). Both have seen an increase in the number of autologous HCT from 2007 to 2018, with a remarkable 137% increase in plasma cell disorders (Table 2). Autologous HCT for AML has declined globally by -42% during this period, but has varied by region, with an increase

(+45%) only in SEAR/WPR. A notable increase was observed in autologous HCT for autoimmune disease (+269%), related to the increase in AMR Latin (+622), EUR (+264) and to a lesser extend in SEAR/WPR and AMR North (both <100%).

The total number of allogeneic HCT has doubled between 2007 and 2018. The indications which showed more than 100% increase during the period were AML, ALL, and MDS/MPN, while the number of allogeneic HCT decreased for CML, CLL, plasma cell disorder, and solid tumors. Among non-malignant diseases, hemoglobinopathies demonstrated a remarkable increase in all regions with a global increase of 329%, highlighted by a high increase of 822% for SEAR/WPR and 571% for AMR North.

Trends by disease stage

AML in first complete remission (CR1) followed by non-CR1 is the most frequent indication for allogeneic HCT. The proportion of non-CR1 is decreased by approximately ten percent globally as a sign that AML are transplanted earlier in their disease stage. Similar applies to ALL, although the amount is approximately five percent. Trends in CML as an overall indication for HCT are decreasing as shown in Tables 1 and 2, but more importantly the proportion of >1st chronic phase (>1CP) in overall CML is approaching 80% in AMR North and SAER/WPR. The proportion in other regions are also high, but below 60%. There is no trend in favor of HCT in earlier stage of the disease. (Figure 4)

Discussion

HCT activity continue to increase worldwide in 2018 and no plateau is detectable in any of the regions. Plasma cell disorder, most commonly multiple myeloma, is the most common indication for autologous transplantation in all WHO regions. The increase in the last decade is remarkable and more pronounced than the increase in patients with lymphoma. During this period, the development of new drugs, including targeted therapies for MM, has

changed the standard treatment algorithm at diagnosis, and autologous HCT remains part of first line treatment.(13-16) A utilization analysis considering the incidence of MM reported a worldwide increase of autologous HCT utilization for MM from 2006 to 2015, but this was limited in high-income regions. (9) Although the overall number of HCT is limited, autoimmune diseases are among the indications with the highest increase rates.(17-19) Regional differences were observed, with Latin America and Europe having the highest number of transplants.(19) Correlation analyses between economic indicators of GNP per capita and per capita total expenditure on health in US dollars and HCT activity showed that the strongest correlation was found for autologous HCT. As discussed earlier, the development of new drugs may have contributed to the increase in the number of autologous HCT, but the rapid launch of new drugs is usually limited to economically affluent countries.

For allogeneic HCT, the most frequent indication in all WHO regions was AML, followed by ALL and MDS/MPN, whose numbers more than doubled in the decade until 2018. (10) Survival outcomes for allogeneic HCT in acute leukemia continue to improve, as studies primarily in leukemia have shown improvement in survival outcomes, with notable decreases in non-relapse mortality over time. (3-5, 20, 21) Thus, allogeneic HCT has become the standard of care in many patients with leukemia especially in diseases with high relapse risk including older patients (22, 23) Allogeneic HCT for nonmalignant disease, including hereditary disease in pediatric patients, showed a more than two-fold increase in this decade. Notable global increase was observed in non-malignant indication (i.e., hemoglobinopathies) for allogeneic HCT, highlighting a growing awareness of its efficacy. (24-28) During the dramatic increase in the number of allogeneic HCT for acute leukemia of more than two-fold, the proportion of non-CR1 at transplant showed gradual decrease in both AML and ALL. The trend shows increased utilization of allogeneic HCT in the earlier disease stages for both AML and ALL. Tyrosine kinase inhibitors (TKIs) treatment has revolutionized the management of CML by effectively inhibiting the BCR-ABL fusion protein, leading to high rates of hematological, cytogenetic, and molecular responses. However, primary and secondary

resistance to TKIs is a significant barrier to optimal outcomes, and factors contributing to response heterogeneity remain unclear. (29) Higher risk of mortality after allogeneic HCT among recipients with CML is reported for recipients of HCT at >1CP with observed >20% decreased survival, and with BCR-ABL1 mutations. (30, 31) Strategies to predict TKI treatment resistance and optimal timing consideration for allogeneic HCT for young patients with CML-CP who manifest resistance to multiple TKI therapies should be followed as proposed in the ELN recommendations. (32)

Donor/stem cell sources that contributed to improved access to allogeneic HCT showed different trends in each WHO region, but all regions were marked by an increase in the percentage of HCT from other related donors, the majority of whom were haploidentical donors. In many countries where the number of siblings is limited, the chance of finding a healthy HLA-identical sibling donor capable of providing hematopoietic stem cells is estimated to be about 25%, and this probability decreases further as the patient population ages. Therefore, increasing the number of HCT from other related donors or unrelated donors is a prerequisite for improving HCT accessibility. HCT from an unrelated donor is a well-studied and well-established treatment with an increasingly favorable outcome, survival outcomes after allele-level HLA matched HCT outcomes are now equivalent to that of HLA identical sibling. (33-36) The matching of HLA at a high-resolution level for unrelated donors has been repeatedly confirmed in studies worldwide, and overall, an HLA single mismatch in HCT from an unrelated donor is considered to reduce survival probabilities by 5 to 10% in the context of calcineurin-inhibitor plus methotrexate GVHD prophylaxis. (37, 38)

An HLA haploidentical donor is a related donor who shares exactly one HLA haplotype and differs by a variable number of HLA genes on the unshared haplotype, and can be found for nearly every patient that is referred for allogeneic HCT. Different approaches to overcome graft-versus-host disease (GVHD) after HLA haploidentical HCT from related donors were reported with reasonable outcomes. (39-41) Lymphocyte replete haploidentical HCT has been developed by using post-transplant cyclophosphamide (PTCy). (42-44) With

its selective depletion strategy of alloreactive lymphocytes, the incidence of acute GVHD, chronic GVHD, and NRM after PTCy-based haploidentical HCT is remarkedly low, thus its use is rapidly increasing (45-47) For allogeneic transplantation, as expected, HCT from unrelated donors showed a strong correlation with the economic indicator of GNP per capita and per capita total expenditure on health. HCT from other related donors showed similar moderate correlation to HCT from HLA-identical sibling donors. Use of unrelated donors for HCT is reported with significant higher cost, even if the costs of stem cell procurement are not included. (48, 49)

In this study, the results of a carefully conducted global HCT activity survey by WBMT, a network of 23 member societies related to HCT, are displayed but some potential limitations remain. Despite all efforts to improve the situation including close collaboration with member societies and workshops conduct, possible gaps of less than 5% for allogeneic HCT and less than 15% for autologous HCT in reporting remain. (8) Succeeding HCTs, i.e., second or third HCT for the same recipient are not considered, since eligibility for Global Activity Data reporting is the first HCT for the recipient in the survey year. Priority is given to feasibility in this Global Transplant Activity data collection, the survey uses simple survey items and does not involve the collection of individual patient level data. Therefore, information available for consideration or comparison are limited. Recipient age is not considered, so the HCT activity analyzed in the study includes recipient of all ages. Activity analyses for specific age groups, such as pediatric or elderly patients, were therefore not performed. For autologous HCT, the age of 75 or younger, and for allogeneic HCT, the age of 65 or younger are generally candidates for HCT recipients. Therefore, the age distribution of the general population may affect the TR: if 10%, 20%, and 30% of the population were 65 years or older, compared to 0% of the population, the TR could be considered as 1.11, 1.25, and 1.43 times higher, respectively. The study was able to include data of HCT up to 2018. Introduction of chimeric-antigen-receptor (CAR)-T cell therapies, novel immune therapies and targeted therapies in late 2010s may change treatment strategies for major indications of

HCT. Global HCT activity survey is being continued by the WBMT, and the impact of these novel therapies for HCT activity in 2019 and beyond will be analyzed in its future studies using the new internet-based registry in a time sensitive way.

In conclusion, increased HCT activity in all WHO regions from 2007 to 2018 was shown. Major indication for autologous HCT is PCD followed by lymphoma, and for allogeneic HCT is AML, followed by ALL and MDS/MPN across WHO regions. Variations in proportion of donor/stem cell source were seen among the WHO regions, all resulted in an increase of access to HCT worldwide.

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Table 1. Absolute number of hematopoietic cell transplantation in 2018 according to indications by WHO regions

	Autologous HCT							Allogeneic HCT							HCT	
	2018						2007	2018						2007	2018	2007
Indications	EUR	EMR AFR	SEAR WPR	AMR North	AMR Latin	Total	Total	EUR	EMR AFR	SEAR WPR	AMR North	AMR Latin	Total	Total	Total	Total
Malignant disease																
Acute myeloid leukemia	273	20	254	30	45	622	1,081	**6,472**	**533**	**5,302**	**3,417**	**586**	**16,310**	**7,359**	**16,932**	**8,440**
Acute lymphoblastic leukemia	68	6	67	11	13	165	177	**2,695**	**315**	**3,125**	**1,416**	**720**	**8,271**	**4,038**	**8,436**	**4,215**
Chronic myeloid leukemia	0	0	1	0	0	1	8	339	46	280	246	99	1,010	1,142	1,011	1,150
MDS/MPN	1	0	3	1	1	6	45	**2,988**	**103**	**1,858**	**1,792**	**206**	**6,947**	**2,569**	**6,953**	**2,614**
Chronic lymphocytic leukemia	10	0	2	8	0	20	115	189	3	31	125	15	363	614	383	729
Other leukemia	0	0	6	7	7	20	35	0	1	208	113	22	344	164	364	199
Plasma Cell Disorder	**12,582**	**699**	**3,793**	**8,114**	**1,565**	**26,753**	**11,267**	403	13	94	52	4	566	828	**27,319**	**12,095**
Lymphoma	**8,279**	**588**	**3,389**	**3,778**	**1,134**	**17,168**	**11,182**	**1,724**	**74**	**877**	**515**	**130**	**3,320**	**2,387**	**20,488**	**13,569**
Solid tumors	**1,468**	**135**	**476**	**668**	**232**	**2,979**	**2,600**	42	5	49	5	7	108	119	**3,087**	**2,719**
Non-Malignant disease																
Bone marrow Failure	5	0	0	0	2	7	2	**791**	**273**	**1,623**	**338**	**251**	**3,276**	**1,310**	**3,283**	**1,312**
Hemoglobinopathy	8	0	2	7	0	17	3	**448**	**283**	**747**	**329**	**20**	**1,827**	**425**	**1,844**	**428**
Primary immune deficiency	7	0	0	13	1	21	5	**601**	**110**	**179**	**261**	**75**	**1,226**	**479**	**1,247**	**484**
Inherited disease of metabolism	6	0	27	6	0	39	5	182	23	81	65	8	359	161	398	166
Autoimmune disease	546	5	54	27	159	791	214	17	3	7	10	1	38	21	829	235
Other non-malignant disease	0	0	1	0	4	5	27	0	6	82	82	16	186	147	191	174
Other disease	19	2	36	9	0	66	39	140	57	44	21	12	274	141	340	180
Total	**23,272**	**1,455**	**8,111**	**12,679**	**3,163**	**48,680**	**26,805**	**17,031**	**1,848**	**14,587**	**8,787**	**2,172**	**44,425**	**21,904**	**93,105**	**48,709**

HCT denotes hematopoietic cell transplantation, MDS denotes myelodysplastic syndromes, MPN denotes myeloproliferative neoplasms, EUR denotes European Region, EMR denotes Eastern Mediterranean Region, AFR denotes African Region, SEAR denotes South-East Asian Region, WPR denotes Western Pacific Region, AMR denotes Region of Americas

Table 2. Percentage increase/decrease of hematopoietic cell transplantation activity from 2007 to 2018 by indication and by region

	Autologous HCT						Allogeneic HCT					
Indications	EUR	EMR/AFR	SEAR/WPR	AMR North	AMR Latin	Total	EUR	EMR/AFR	SEAR/WPR	AMR North	AMR Latin	Total
Malignant disease												
Acute myeloid leukemia	-56	-55	+45	-84	+2	-42	+107	+160	+176	+72	+343	+121
Acute lymphoblastic leukemia	-32	+500	+17	-15	+160	-6	+61	+133	+155	+59	+449	+104
Chronic myeloid leukemia	-100	–	+0	–	-100	-87	-11	-47	-30	+18	+62	-11
MDS/MPN	-96	-100	-50	-85	+0	-86	+125	+139	+267	+179	+274	+170
Chronic lymphocytic leukemia	-90	-100	+100	+33	-100	-82	-41	+200	+181	-54	+275	-40
Plasma Cell Disorder	+96	+429	+180	+164	+384	+137	-19	+8	+40	-78	-50	-31
Lymphoma	+32	+121	+79	+39	+158	+47	+53	+393	+81	-33	+195	+34
Solid tumors	+4	+400	+3	+2	+354	+14	-23	+400	+11	-73	–	-9
Non-Malignant disease												
Bone marrow Failure	–	–	–	–	–	–	+80	+92	+352	+31	+122	+150
Hemoglobinopathy	–	–	–	–	–	–	+146	+164	+822	+571	+233	+329
Primary immune deficiency	–	–	–	–	–	–	+154	+144	+219	+110	+316	+155
Inherited disease of metabolism	–	–	–	–	–	–	+142	+283	+237	+27	+60	+122
Autoimmune disease	+264	–	+92	+92	+622	+269	+54	+50	+133	+100	–	+80
Total	+53	+203	+122	+89	+260	+81	+79	+128	+172	+55	+271	+102

HCT denotes hematopoietic cell transplantation, EUR denotes European Region, EMR denotes Eastern Mediterranean Region, AFR denotes African Region, SEAR denotes South-East Asian Region, WPR denotes Western Pacific Region, AMR denotes Region of Americas

Table 3. Correlation of macroeconomic factors with hematopoietic cell transplantation activity in 2018

	GNI per capita (US$)		General government expenditure on health (%)		Total expenditure on health of GDP (%)		Per capita total expenditure on health (US$)		Government expenditure in total expenditure on health (%)	
	r	p value	r	p value	r	p value	r	p value	r	p value
Autologous HCT	0.79	<0.001	0.46	<0.001	0.60	<0.001	0.80	<0.001	0.55	<0.001
Allogeneic HCT	0.66	<0.001	0.46	<0.001	0.58	<0.001	0.67	<0.001	0.47	<0.001
Allogeneic HCT from HLA-identical sibling donors	0.48	<0.001	0.34	0.001	0.40	0.001	0.47	<0.001	0.34	0.001
Allogeneic HCT from other related donors	0.45	<0.001	0.39	<0.001	0.47	<0.001	0.45	<0.001	0.31	0.004
Allogeneic HCT from unrelated donors	0.68	<0.001	0.45	<0.001	0.59	<0.001	0.70	<0.001	0.49	<0.001

US$ denotes United States dollar, GDP denotes Gross Domestic Product, HCT denotes hematopoietic cell transplantation, HLA denotes human leukocyte antigen

Figure legends

Figure 1. **Hematopoietic cell transplantation (HCT) activity per 10,000,000 population (i.e., transplant rate, TR) for HLA identical sibling HCT, haplo-identical related HCT, HCT from unrelated donors, and unrelated cord blood transplantation (CBT) in 2018.**

The numbers of countries with more than 25 (or more than 50) TR for HLA identical sibling HCT (A), other related HCT (B), HCT from unrelated donors (C), and unrelated CBT (D) were 45 (25), 26 (8), 37 (33), and 2 (1), respectively.

Figure 2. **Correlation between economic indicators and hematopoietic cell transplantation (HCT) activity.**

Correlations between economic indicator of gross national income (GNI) per capita and autologous (A) and allogeneic (B) HCT activity per 100,000 population were observed (correlation coefficient [r]=0.79, and 0.66 for autologous and allogeneic, respectively). Among allogeneic HCT, HCT from HLA-identical sibling donors (C, r=0.48) and HCT from other related donors (D, r=0.45) showed moderate correlation, and HCT from unrelated donors showed strong correlation (E, r=0.68).

Figure 3. **Trend of the numbers of allogeneic hematopoietic cell transplantation (HCT) from HLA identical sibling donors, other related donors, or unrelated donors by WHO regions.**

Allogeneic HCT from HLA identical siblings has seen limited growth from 2007 to 2018. (A) HCT from other related donors increased from 2007 to 2018 in all regions. (B) Trend of HCT from unrelated donors differed among regions. (C) The global trend of unrelated

cord blood transplantation showed decrease since 2011 in all regions except South-East Asian Region and Western Pacific Region (SEAR/WPR). (D)

Figure 4: **Trend of disease stage at transplant for acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and chronic myeloid leukemia (CML).**
The proportion of non-first complete remission (CR1) is decreased by approximately ten percent globally as a sign that AML are transplanted earlier in their disease stage. (A) Similar applies to ALL, although the amount of decrease in the proportion of non-CR1 is approximately five percent. (B) Trends in the proportion of >1st chronic phase (>1CP) in overall CML is approaching 80% in Region of Americas (AMR) North and South-East Asian Region and Western Pacific Region (SEAR/WPR), followed by 50-60% in other regions. (C)

Figure 1

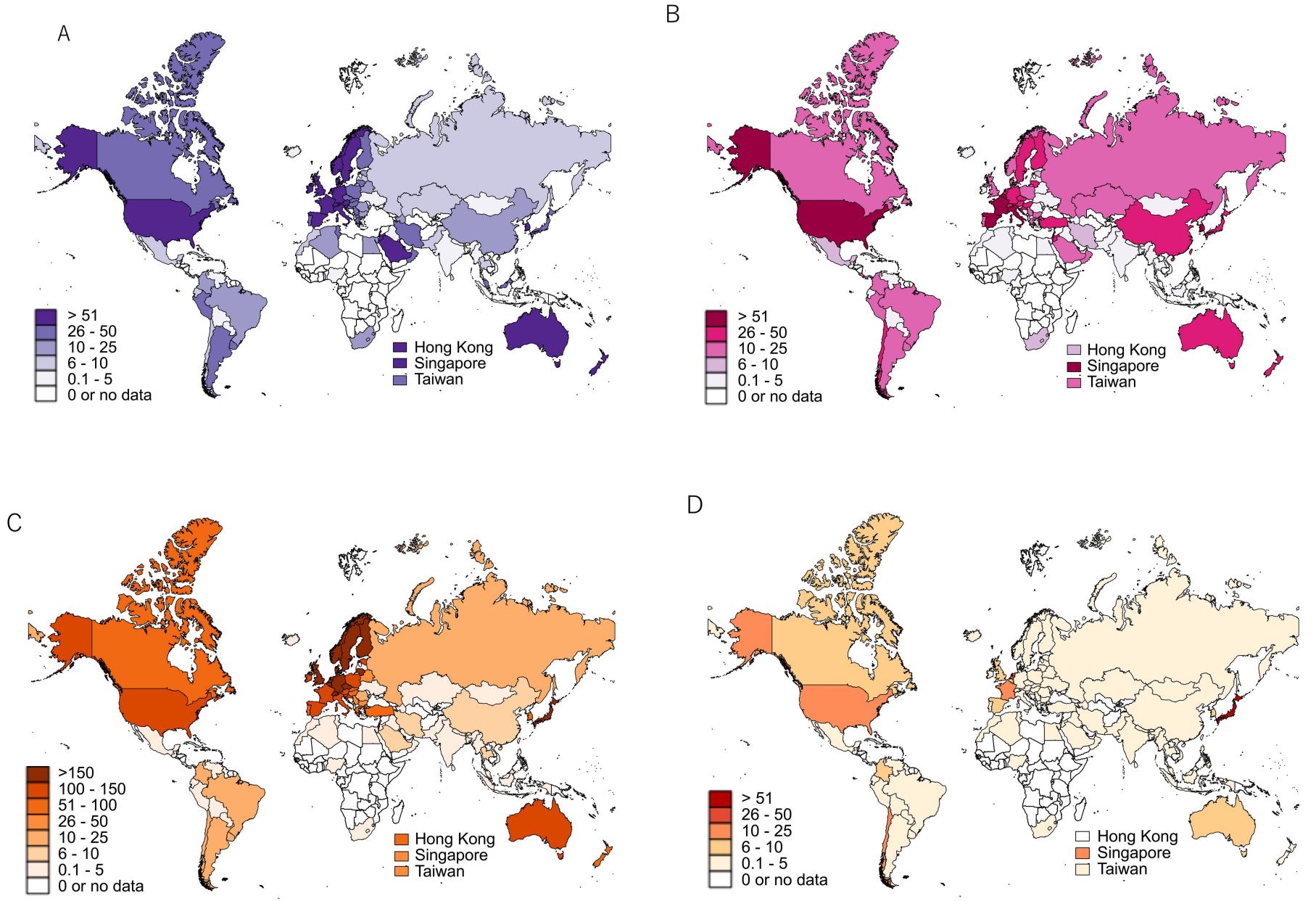
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Fig2

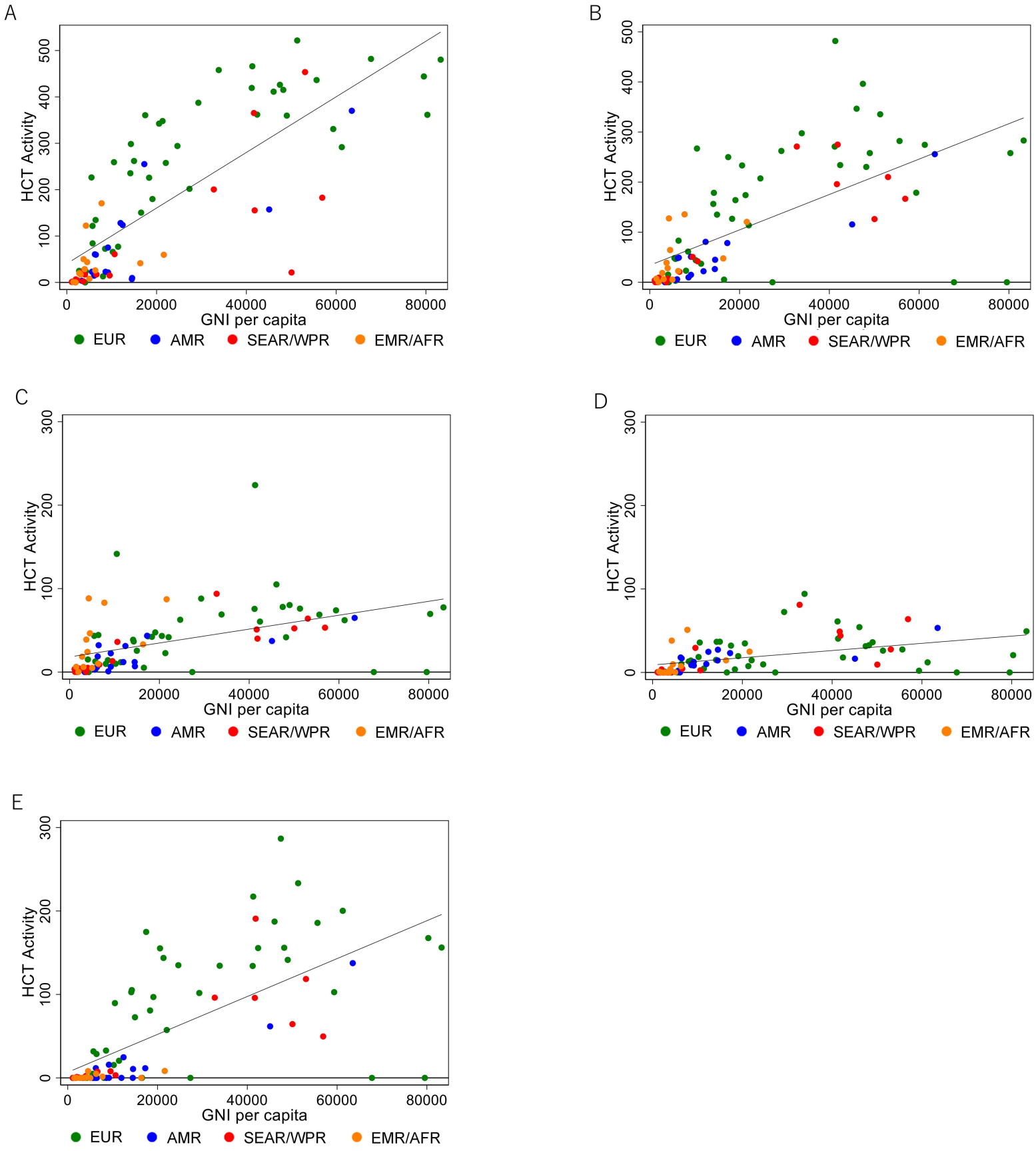
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Fig3

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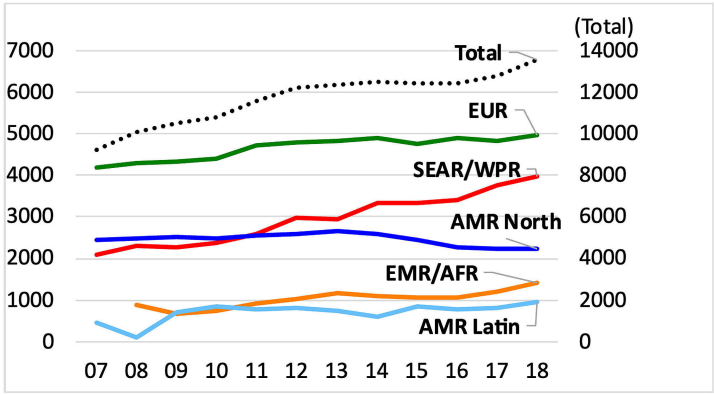
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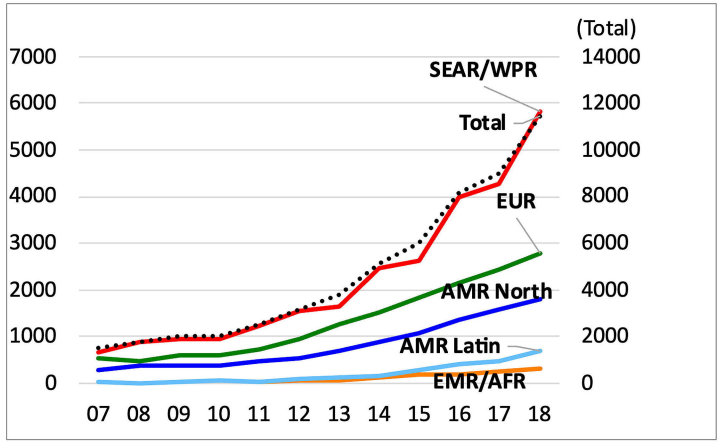
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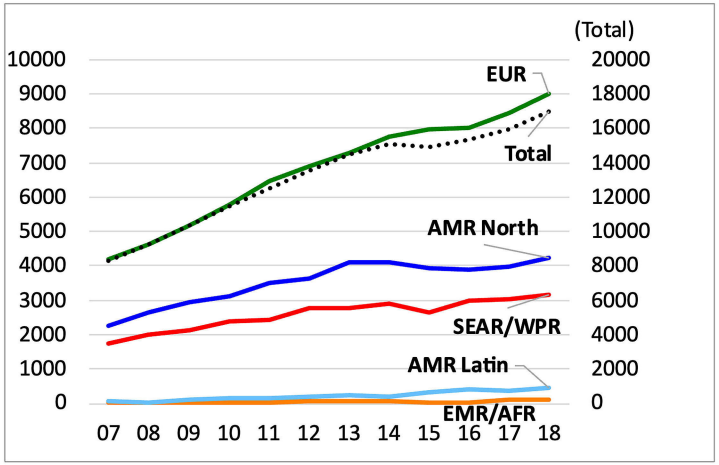
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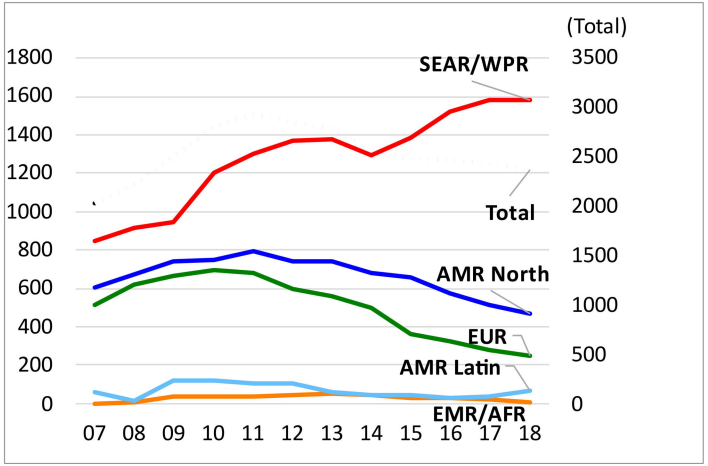
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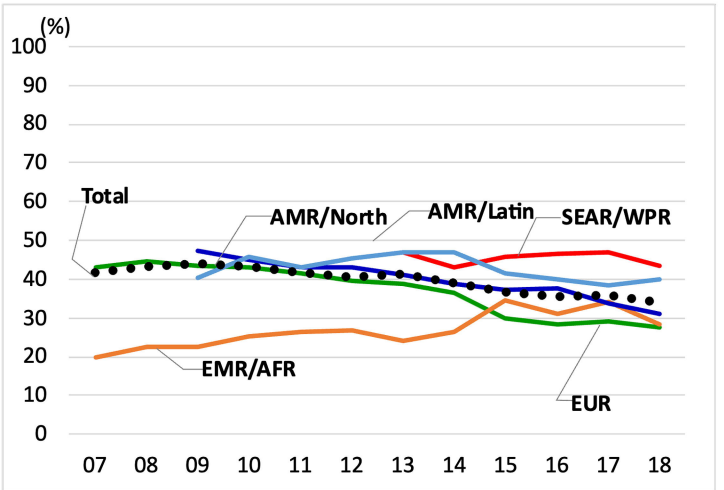
Fig4

A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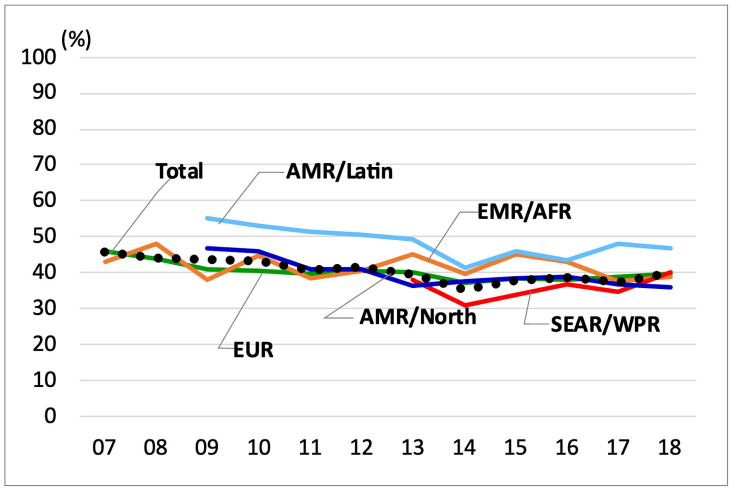
B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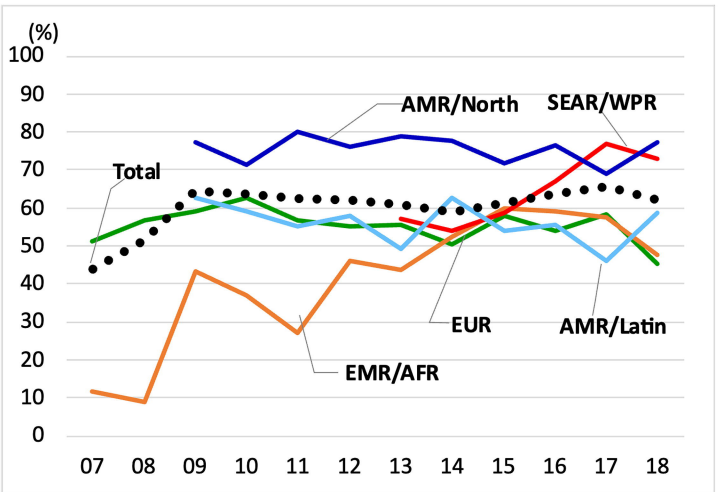
C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Supplementary Method

Data collection and validation

Global transplant numbers by country of origin, year of transplant, disease and donor type (autologous vs. allogeneic) are collected since 2006 in 194 WHO member states through the registries of the reporting member organizations, or national registries or transplant centers directly either in paper form or electronically using the standardized WBMT form. Detailed and validated information about main indication including stage of the disease, stem cell source, and allogeneic (family matched, family mismatched and unrelated) donor type was obtained for the years 2006 to 2018. Since 2007, reports on HCT activity from all WHO regions are being continued. Data were validated by a range of different independent systems; through confirmation by the reporting teams, following receipt of a computer printout of the entered data, by selective comparison with MED-A/TED datasets in the EBMT or CIBMTR data system or by crosschecking for double reporting with national registries. Data were validated by onsite visits to selected teams to verify reported data as part of the quality control program within the European, North American, Latin American and Asia-Pacific organizations. On-site visits to selected teams were part of the quality-control accreditation program of JACIE (www.ebmt.org/jacie-accreditation) or FACT (www.factweb.org). Based on quality

controls and contacts with regulatory agencies or national offices, the response rate for allogeneic HCT was estimated to be >95% and for autologous HCT 80–90%. The number of potential missing transplant numbers is estimated to be less than 5% for allogeneic HCT and less than 15% for autologous HCT. This number is much lower for Australia, Canada, Europe, Japan, and the USA. The survey focuses on the numbers of patients treated for the first time with HCT in the year of survey.

Definitions of the macroeconomic indicators

General government expenditure on health as a percentage of total government expenditure is defined as the level of general government expenditure on health and is expressed as a percentage of total government expenditure. Total expenditure on health as a percentage of gross domestic product (GDP) is defined as the level of total expenditure on health expressed as a percentage of GDP, where GDP is the value of all final goods and services produced within a nation in the given year. Per capita total expenditure on health is defined as the per capita total expenditure on health, expressed at the average exchange rate for that year in US$. Government expenditure in total expenditure on health is defined as the level of government expenditure on health and

is expressed as a percentage of total health expenditure. The values obtained for GNI per capita and per capita total expenditure on health of year 2018 are in US dollars.

Statistical analysis

Descriptive statistical analysis was performed to assess HCT activity per WHO regions, indications, and donor type/stem cell source. Delta, or percentage of increase or decrease during a calendar-year period is calculated by the subtraction of the number of HCT of the first year from the last year of the period divided by the number of HCT of the first year. The cutoffs of TR were determined by considering the percentile values. All analyses were performed using Stata® version 17 (Stata Corporation, College Station TX, USA). World Bank databases were accessed by using a Stata module, “wbopendata” version 16.3. Pearson’s correlation coefficient was calculated between the GNI per capita and country-level HCT activity per 10 million population. Graphical procedures were done by using Stata® version 17 or Microsoft® Excel® of Microsoft 365.

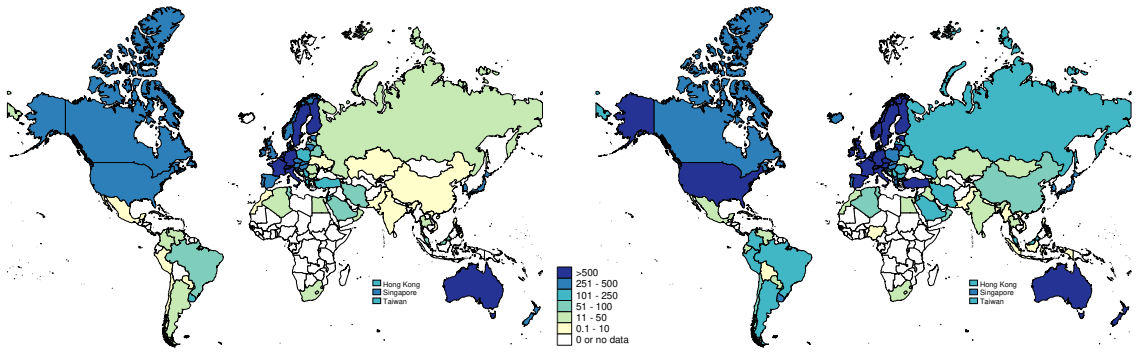
Supplemental Figure legends

Supplemental Figure 1. **HCT activity per 100,000 population for 2007 and 2018**

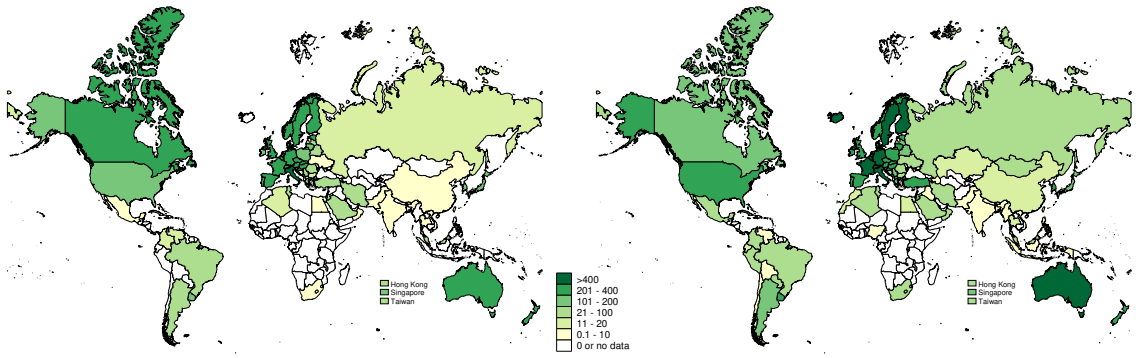
The number of HCT per 100,000 population on the same scale for 2007 and 2018, showing increasing trend in the number of HCT per population for all (A), autologous (B), allogeneic (C), related (D), and unrelated (E) HCT in all regions of the world. Team density per 100,000 population in 2007 was 4.92 (median, 25th and 75th percentile, 0.94 and 9.58) and 3.69 (median, 25th and 75th percentile, 1.09 and 8.50) in 2018 (F).

Supplemental Figure 1.

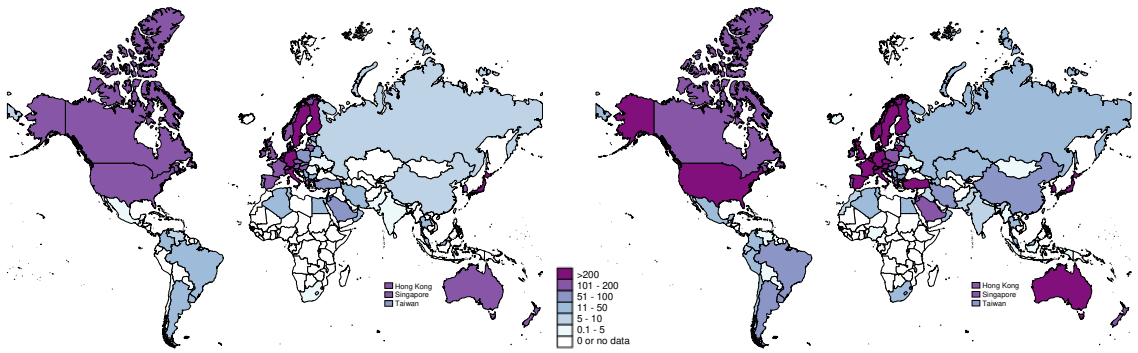
A. Total HCT in 2007 (left) and 2018 (right)



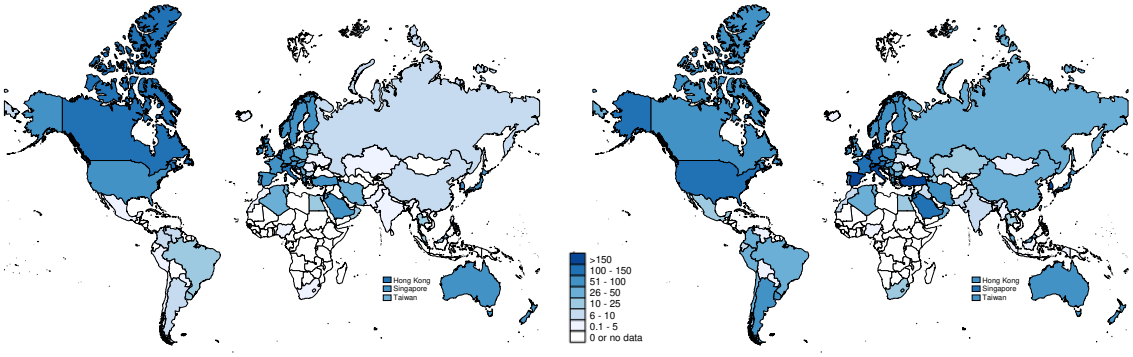
B. Autologous HCT in 2007 (left) and 2018 (right)



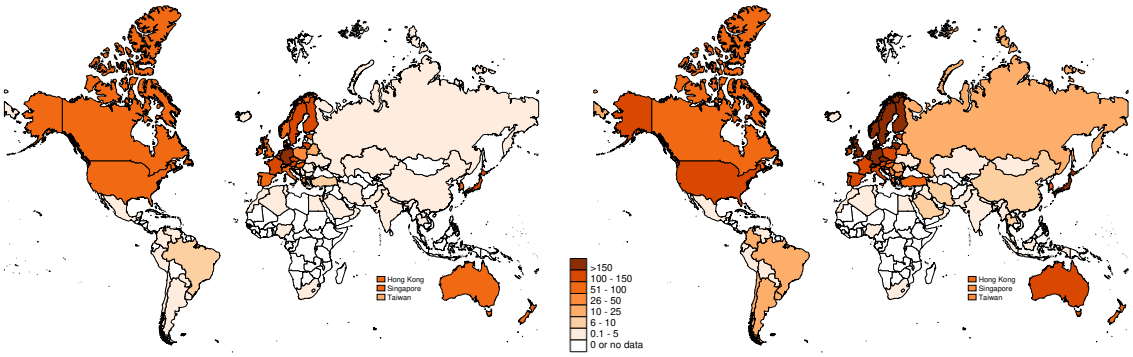
C. Allogeneic HCT in 2007 (left) and 2018 (right)



D. Allogeneic HCT from related donors in 2007 (left) and 2018 (right)



E. Allogeneic HCT from unrelated donors in 2007 (left) and 2018 (right)



F. HCT team density in 2007 (left) and 2018 (right)