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# Hematopoietic stem cell transplantation A Global Perspective

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## Abstract

**Context—**Hematopoietic stem cell transplantation (HSCT) requires significant infrastructure. Little is known on its use and the factors associated with it on a global level.

**Objective—**To determine current use of HSCT, to assess differences in its application and to explore associations of macroeconomic factors with transplant rates on a global level.

**Design—**Structured worldwide collection of numbers of allogeneic and autologous HSCT by main indication, donor type and stem cell source for the year 2006.

**Setting—**Worldwide Network for Blood and Marrow Transplantation (WBMT), a global non-profit umbrella organization for clinical HSCT.

**Patients—**All patients with an allogeneic or autologous HSCT for any indication transplanted in 2006 within any of the participating countries.

**Interventions—**none

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**Authorship** Contribution: A.G., D.N., M.H. and Y.K. designed the study concept. M.A., M.C.P., L. F. B., A. Y., J. S. and J.L. were responsible for the organization of the data. H.B. was responsible for the data collection. A. S., M.G. and K.F performed the data analysis. All authors contributed to the writing and approved the final manuscript.

There are no conflicts of interest pertinent to this manuscript to declare.

**Main Outcome measures—**Transplant rates (number of HSCT per 10 million inhabitants) by indication, donor type and country; description of main differences in HSCT use; macroeconomic factors of reporting countries associated with transplant rates.

**Results—**There were 50'417 first HSCT, 21'516 allogeneic (43%), 28'901 autologous (57%) reported from 1'327 centers in 71 countries for leukemia (17'049 (34%; 89% allogeneic)), lymphoma (27'492 (54%; 87% autologous)), solid tumors (2'925 (6%, 95% autologous)), non-malignant disorder (2'593 (5%; 92% allogeneic)) or, "others" 358 (1%). Use of allogeneic or autologous HSCT, use of unrelated or family donors for allogeneic HSCT and proportions of disease indications varied significantly between countries and continental regions. In linear regression analyses, Government Health Care Expenditures ($r^2$ = 77.33), team density ($r^2$ =76.28), Human Development Index ($r^2$ = 74.36) and Gross National Income /Capita ($r^2$ = 74.04) showed the highest association with transplant rates.

**Conclusions—**HSCT is an accepted therapy today with different use and needs worldwide. Availability of resources, Governmental support and, access for patients to a team were identified as key factors for higher transplant rates.

### Keywords

Hematopoietic stem cell transplantation; Global perspective; transplant rates; leukemia; lymphoma; solid tumors; non-malignant disorders; Gross National Income per capita; Human Development Index

## INTRODUCTION

Transplantation of hematopoietic stem cells (HSCT) has become the standard of care for many patients with defined congenital or acquired disorders of the hematopoietic system or with chemo- radio- or, immuno- sensitive malignancies (1-3). Over the last two decades, HSCT has seen rapid expansion and a constant evolution in technology use. Novel indications are currently in evaluation (4-5). Bone marrow is supplemented as stem cell source by peripheral blood or cord blood. More than 14 million typed volunteer donors or cord blood units from the many registries worldwide (www.worldmarrow.org) provide stem cells for patients without family donors. Novel conditioning regimens with lower intensity have expanded the use of HSCT to older patients or to those with co morbidities (6-9).

Still, HSCT remains associated with significant morbidity and mortality and represents one example of high cost, highly specialized medicine. It requires significant infrastructure and a network of specialists from all fields of medicine. Hence, information on indications, use of specific technologies and trends is essential for correct patient counseling and for health care agencies in order to prepare the necessary infrastructure and to avoid planning errors (10-13). In addition, HSCT is no longer limited to countries with abundant resources. Indeed, HSCT might represent the most cost effective therapy in some countries (14). An assessment of global transplant activity is warranted. In view of the growing numbers of transplant teams and HSCT worldwide and the rising awareness of the need for a global perspective for all cell, tissue and organ transplants by the World Health Organization (www.who.int) (15) the recently founded Worldwide Network for Blood and Marrow Transplantation - WBMT (www.wbmt.org) decided to collect standardized HSCT activity data on a global level. Results of this first worldwide survey are presented here.

# PATIENTS AND METHODS

## Study design

This is a retrospective survey amongst all HSCT teams known to the investigators, organized by WBMT through established international or regional organizations. The study was approved by the Ethics Committee of the University of Basel; the need for informed consent of patients was waved since no individualized information is transferred.

## Participating Groups, Continents, Countries and Teams

1327 teams in 71 reporting countries over 5 continents (eTable 1) provided information on their numbers of HSCT in the year 2006 by indication and donor type (Table 1) (16). They were subdivided into 4 regions, based on the WHO regional offices classification (www.who.int/about/regions/en/): America (WHO regions North- and South America), Asia (WHO regions "South East Asia and Western Pacific Region which includes Australia and New Zealand), Europe (includes Turkey and Israel) and, EMRO/Africa (WHO regions Eastern Mediterranean and Africa).

Data were provided by the Asian Pacific Blood and Marrow Transplant Group APBMT (www.apbmt.org), the Australian Bone Marrow Transplant Recipient Registry ABMTRR (www.bmtnsw.com.au), the Canadian Blood and Marrow Transplant Group CBMTG (www.cbmtg.org), the Center for International Blood and Marrow Transplantation CIBMTR (www.cibmtr.org), the Sociedade Brasileira de Transplante de Medula Ossea SBTMO (www.sbtmo.org), the Eastern Mediterranean Blood and Marrow Transplant Group EMBMT (www.embmt.org) and, the European Group for Blood and Marrow Transplantation EBMT (www.ebmt.org) (eTable 1) (17-20).

## Collection system and data validation

Data were obtained from the mandatory reporting system of initial transplant data (ABMTRR, CBMTG, CIBMTR) or collected on separate survey data forms from individual centers or national registries (APBMT, EBMT, EMBMT, SBTMO).

Data were validated by different independent systems; through confirmation by the reporting team, which received a computer printout of the entered data, by selective comparison with MED-A data sets in the EBMT ProMISE (http://www.msbi.nl/Promise/) data system (EBMT) or by crosschecking with National Registries. Onsite visits of selected teams were part of the quality control program within CIBMTR and EBMT teams.

## Definitions

**Transplant numbers—**This WBMT survey focused on the numbers of patients treated for the first time with HSCT in 2006. Information on *additional* transplants, e.g. r*e-transplants* or m*ultiple transplants* (21) was not included.

**Transplant rates—**Transplant rates were computed as the number of HSCT per 10 million inhabitants (21). Transplant rates refer to the number of transplants in a given country compared to its own population, without adjustments for patients who cross borders and receive their HSCT in a foreign country. Population data were obtained from the US census office (http://www.census.gov).

**Team density—**Team density refers to the number of transplant teams per 1 million inhabitants (22).

**Economic factors—**Transplant rates within the reporting participating countries were compared with a range of macroeconomic health care indicators: Gross National Income per Capita (GNI/cap), Total Health Care Expenditures, Governmental Health Care Expenditures, adult, infant and maternal mortality rate, number of hospital beds per capita, caesarean section rates, Human Developmental Index and, team density. Data were obtained from the worldbank (www.worldbank.org), WHO (www.who.int) and the United Nations (http://hdr.undp.org). Data from the year 2006 were used whenever available for all comparisons.

### Statistical analysis

The association of the macro-economic factors with transplant rates was estimated by single linear and multiple linear regression analysis, using the ordinary least square method. The linear relation, positive or negative, between macro-economic factors and transplant rates after transformation was measured by t-statistics; a level of 5% was considered as significant. The goodness of fit was measured by the coefficient of determination (r-squared, $R^2$). For the single and multiple linear regression analysis the dependent variables were transformed in order to point out the linear associations. In the multiple regression, all factors were assessed for their multicollinearity. Taiwan and Hong Kong were excluded from the multiple economic comparisons because of missing information on Governmental Health Care expenditures. Cesarean section rates were included in the single linear but not the multiple regression analysis because data from too many countries were missing.

The hypothesis tests for comparing the means of two independent samples (t-Test, level of significance = 5%) was used to evaluate, if the four world regions had a significant difference in the relative proportion of main indications and donor type (allogeneic vs. autologous, un-related vs. family donors).

## RESULTS

### Numbers of HSCT, main indications and donor type

A total 50’417 transplants, 22’516 (43%) allogeneic and 28’901 (57%) autologous were reported for 2006 (Table 1). Main indications were *lymphoproliferative disorders* (27’492 patients (54%); 3’502 allogeneic (13%), 23’990 autologous (87%) HSCT); *leukemias* (17’049 patients (34%); 15’210 allogeneic (89%), 1’839 autologous (11%) HSCT; *solid tumors* (2’925 patients (6%); 153 allogeneic (5%), 2’772 autologous (95%) HSCT); *non-malignant disorders* (2’593 patients (5%); 2’396 allogeneic (92%), 197 autologous (7%) HSCT) and *other non specified disorders* (358 patients; 1%).

The most frequent malignancy as indication for an allogeneic HSCT was acute myeloid leukemia (7’026 HSCT; 33%). The most frequent indication for a non-malignant disease was a bone marrow failure syndrome (1’336 HSCT; 6%). The most frequent indication for an autologous HSCT was a plasma cell disorder (11’877 HSCT; 41%) (Table 1).

The 50’417 HSCT were unequally distributed over the four regions with 17’875 in America (36%; median 61 HSCT per country, range 8 to 15082), 7’096 in Asia (14%; median 139 HSCT per country, range 5 to 3823), 24’216 in Europe (48%; median 255 HSCT per country, range 6 to 4619), and 1’230 in EMRO/Africa (2%; median 63 per country, range 10 to 360). The absolute numbers in the participating countries ranged from 15’082 HSCT (USA) to 5 (Vietnam) or to no HSCT.

### Transplant rates in 2006

Transplant rates were significantly different between the four continental regions with a median of 48.5; range 2.5 to 505.4 in the Americas, median 184, range 0.6 to 488.5 in Asia, median 268.9, range 5.7 to 792.1 in Europe and 47.7 median, range 2.8 to 95.3 in EMRO/Africa.

The transplant rates varied between the participating countries from 792 total HSCT per 10 million inhabitants in Israel to 0.6 HSCT in Vietnam (Figure 1), from 434.9 allogeneic HSCT per 10 million inhabitants in Israel to 0.2 in Vietnam and, from 500 autologous HSCT per 10 million inhabitants in Iceland to 0.3 in Mexico.

### Regional differences in donor type and main indications

Overall, there were more autologous (28'901, 57%) than allogeneic (21'516, 43%) HSCT (Table 2). This was seen in America and Europe but not in Asia (57% allogeneic HSCT) and EMRO/Africa (65% allogeneic HSCT) (Figure 2). The differences between Asia and America (t-stat 3.340, t crit 2.160 and p =0.005), Asia and Europe (t-stat 4.244, t crit 2.201 and p =0.001) as well as between America and Africa/EMRO (t-stat -4.214, t crit 2.228 and p =0.002) or Europe and Africa/EMRO (t-stat -4.963, t crit 2.228 and p =0.001) were highly significant but not between America and Europe ((t-stat 1.664, t crit 2.101 and p =0.113).

The proportion of unrelated donor HSCT was highest in Asia (2'110, 52%); it was negligible in EMRO/Africa (0.7%) (Figure 2). These differences in unrelated versus family donors were significant between America (t-stat -10.00, t crit 2.23 and p =0.000), Asia (t-stat -8.403, t crit 2.201 and p =0.000) or Europe (t-stat -13.309, t crit 2.017 and p =0.000) and Africa/EMRO but not between America and Europe (t-stat 0.15, t crit 2.11 and p =0.88).

Leukemia was the main indication for allogeneic HSCT globally (71%; Americas 69%, Asia 77%, Europe 71%, EMRO/Africa 61%). Non-malignant diseases comprised about 10% in America, Asia and Europe, near 35% in EMRO/Africa (figure 2). Lymphoma was the most common indication for autologous HSCT in EMRO/Africa (79%), plasma cell disorders in America and Europe. There were more allogeneic HSCT for chronic myelogenous leukemia (28%), and hemoglobinopathies (26%) in EMRO/Africa compared to Asia (chronic myeloid leukemia 7%, hemoglobinopathies 11%).

### Transplant rates and macroeconomic factors

No transplants were performed in countries with less than 300 000 inhabitants, less than 960 $km^2$ or, less than 680 US$ GNI per capita. Beyond these values, all macro-economic factors had a significant positive (all others) or negative (mortality ratios) association with transplant rates ($p<0.05$; t-test) with a widely variable explanatory content: Gross National Income per Capita ($r^2= 74.04$), Total Health Care Expenditures ($r^2= 73.41$), Governmental Health Care Expenditures ($r^2= 77.33$) (Figure 3a), adult ($r^2= 49.03$), infant ($r^2= 66.31$) and maternal mortality rate ($r^2= 63.21$), hospital beds ($r^2= 32.04$), caesarean section rates ($r^2= 30.56$), team density ($r^2= 76.28$) (Figure 3b) and Human Developmental Index ($r^2= 74.36$) (Figure 3c).

In the multiple linear regression analysis, the first factor with the best explanatory content, 'government health care expenditure' (GOV), explained 77.33% of the variance of the transplant rates. The second factor 'team density' (TD) raised $R^2$ to 79.83%, the third factor 'GNI/cap' (GNI) added another 4.41% of explanation. All other factors, including the Human Development Index, became insignificant, mainly due to multicollinearity with GNI/cap, meaning that several factors did correlate highly with each other. The equation of the

multiple regressions was therefore: $\sqrt{TR} - c_1 \sqrt{GOV} + c_2 \ln(TD) + c_3 \ln(GNI)$. Hence, combined explanatory content was $R^2 = 84.24$.

## DISCUSSION

This first WBMT report documents the current state of HSCT on a global level. It describes the achievements, illustrates the major differences and points to the key needs. Transplant activity is concentrated in countries with higher governmental health care expenditures, higher GNI/capita and higher team density. Hence, availability of resources, governmental support and, access to a transplant center are the key factors related to regional transplant activity. In short, resources are required to perform HSCT, HSCT teams need support and, patients have to have access to the procedure. This statement includes, that disease prevalence can differ between regions and could contribute to differences in transplant rates; these data were not included in this report.

The close link of transplant rates with GNI/capita has been recognized many years ago; HSCT is an expensive procedure with a substantial investment for a single patient (21). Below a minimum national income, a threshold of about 700 US$ GNI/cap was identified, no transplants were performed. However, GNI/capita explained only parts of the variations. We were therefore specifically interested in other macroeconomic factors associated with transplant rates. These factors were chosen with intention. They were either directly linked to availability of resources (GNI/capita, Health care expenditures), to governmental support (governmental health care expenditures) or, to the overall infrastructure in a country (human development index). Others reflect quality measures of the health care system (mortality rates) or indicate potential overuse of the health care system (hospital beds, cesarean section). The results were clear. Of all macroeconomic factors, the report identified Governmental Health Care Expenditures as the most closely associated factor with transplant rates; hence, as strongest factor for establishing and developing a transplant network within a country. The report could not assess the role of the health care system in the participating countries; there is no globally accepted definition available. The report cannot give explanations, but some assumptions can be made. The strong association with governmental health care expenditures might be in part explained by the substantial number of HSCT in middle income countries where HSCT compares favorably in cost effectiveness with conventional treatment for patients with chronic diseases and expensive drug therapies. Transfusions and iron chelating therapy for hemoglobinopathies or tyrosine kinase inhibitor treatment for chronic myeloid leukemia can equal costs for a transplant within one or two years of treatment (15). The higher proportion of non malignant disorders and chronic myeloid leukemia in the EMRO/Africa region where the vast majority of countries belongs to the middle or low income category are in support of this interpretation.

Transplant rates were strongly associated with team density. There was no indication for saturation in this association. Hence, a minimum number of transplant teams per inhabitants must be available that patients have sufficient access. However, teams appear not to overuse their infrastructure (22). Data are insufficient to define an “optimal” number of transplant teams per inhabitants but clearly more than one in ten million appears appropriate.

The very weak association of transplant rates with hospital beds or cesarean section rates indicates further that HSCT were principally performed out of need, not because of availability of an infrastructure. None of the other traditional health care indicators or the composite Human Development Index provided a higher explanatory content or did add information in multiple regression analysis.

There were significant differences between the regions concerning indications and donor type with fewer autologous HSCT in Asia and EMRO/Africa than in America and Europe. There were more unrelated donor HSCT in America, Asia and Europe than in EMRO/Africa, with the highest proportion of unrelated HSCT in Japan. There were also more HLA identical sibling donor HSCT for congenital disorders or for aplastic anemia in countries with limited resources. There is a likely explanation. As mentioned above, an allogeneic sibling donor HSCT for a patient with aplastic anemia, thalassemia or severe combined immune deficiency might be the most cost efficient way of therapy in a country with some but still limited resources and a sibling donor might represent the most readily available inexpensive stem cell source (15,23).

There are some limitations of this report; they warrant caution in interpretation. The organizations collecting data had neither legal enforcement to obtain nor the possibility to control all data locally for accuracy and completeness. Cross checks with national organizations indicate that the report covers near 100% of all HSCT in countries with a national transplant organization. From other countries we know that information is not complete. A few countries choose not to report any data. Most missing information relates to numbers of autologous HSCT. They are performed in some countries outside national transplant organizations and frequently in non-university institutions. Despite these limitations, the main observations of this report on main indications, donor type, transplant rates and associations with macro-economic factors should remain valid. Finally, the report has no information on outcome of the transplant procedures nor on correctness of the indication; this is beyond the scope of this article and would require a much longer follow-up time (24).

The report was in part triggered by the rising awareness of scientific and health care organizations including the World Health Organization to address key aspects of cell, tissue and organ transplantation on a global level. (http://www.who.int/ethics/topics/transplantation_guiding_principles/en/index.html). In contrast to solid organ transplantation, HSCT faces other limitations than donor organ shortage (25). Patients are in need of a closely matched donor, family or unrelated donor, who might be available anywhere in the world. The many unrelated donor registries and public cord blood banks work in a global framework. In 2008, there were, for the first time, more unrelated donor than family donor transplants (www.EBMT.org) and more unrelated transplants across than within borders (www.worldmarrow.org). In addition to traditional HSCT, novel treatment forms with hematopoietic stem cells for non-hematopoietic use or transplantation of non hematopoietic stem cells for organ and tissue repair are under investigation (26-29). The challenges with these new forms of therapy have recently been addressed; stem cell tourism has become a topic of concern (30). Information on current status has become a necessity for correct patient counseling and health care planning.

In conclusion, this first global overview on HSCT activity demonstrates that HSCT is an accepted therapy worldwide today, with different needs and priorities in different regions. Transplant activity is concentrated in countries with higher health care expenditures, higher GNI/capita and higher team density; hence, availability of resources, governmental support and, access to a transplant center determine regional transplant activity. These data provide a solid basis for up-to-date health care counseling and targeted interventions and support the establishment of comprehensive regional registries.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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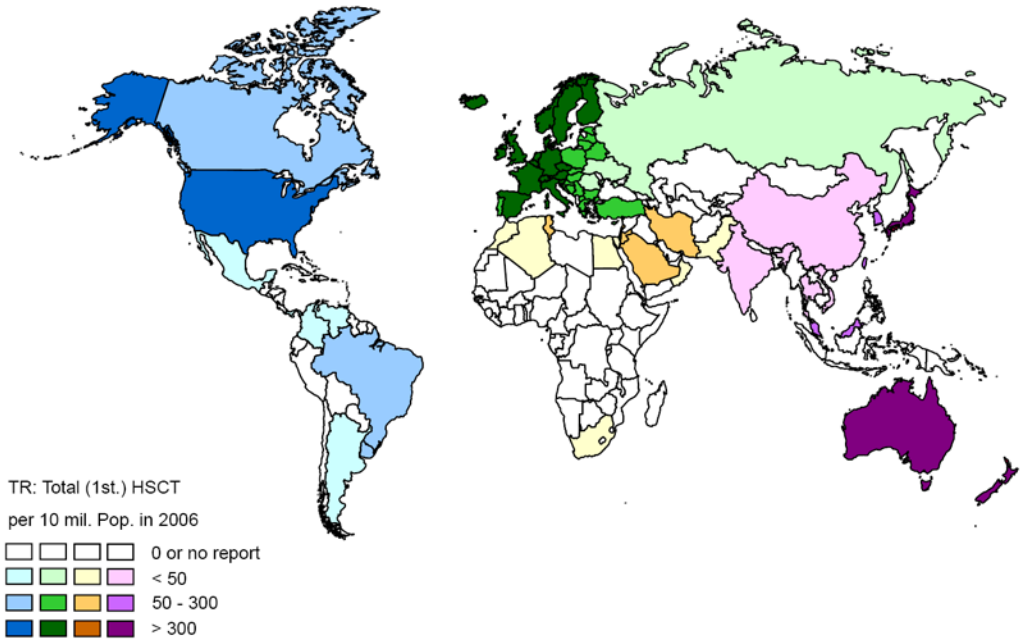


**Fig 1. Global distribution of HSCT in 2006**

Transplant rates (= number of HSCT per 10 million inhabitants) for all HSCT, allogeneic and autologous by continental region.

Regions are colored by WHO regional offices code (see text) (www.who.int/about/regions/en/). Blue: Americas; green: Europe; magenta: Asia; yellow: EMRO/Africa

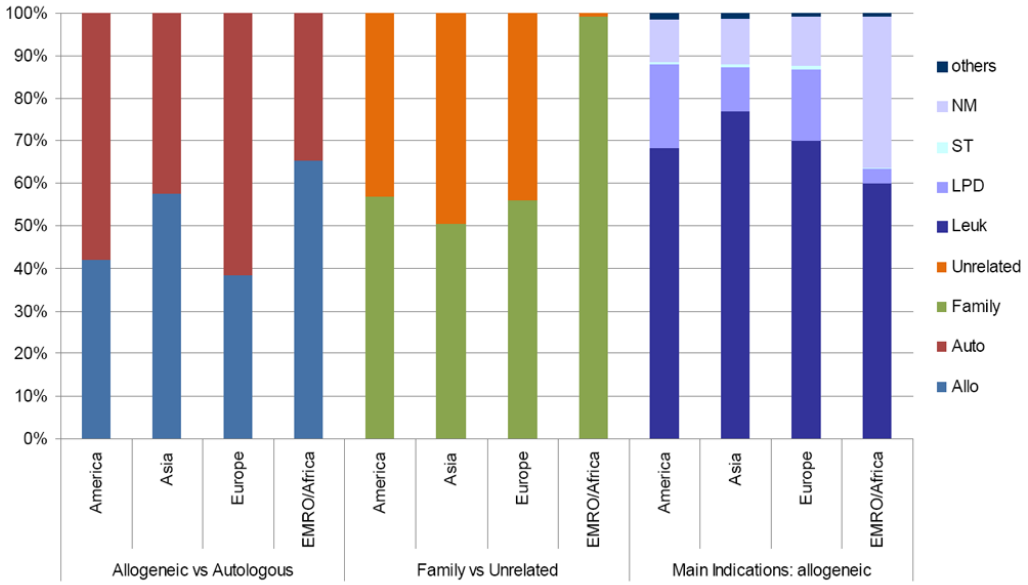


**Fig 2. Relative proportion of donor type and main indications by continental region**

Proportion of allogeneic versus autologous HSCT (left four bars)

Proportion of family versus unrelated donors in allogeneic HSCT (middle four bars)

Proportion of main indications for allogeneic HSCT (right four bars)

Leuk = leukemia, LPD = lymphoproliferative disorders, NM = Non malignant disorders, ST = solid tumors

Auto= autologous HSCT; allo = allogeneic HSCT

Figure 3a

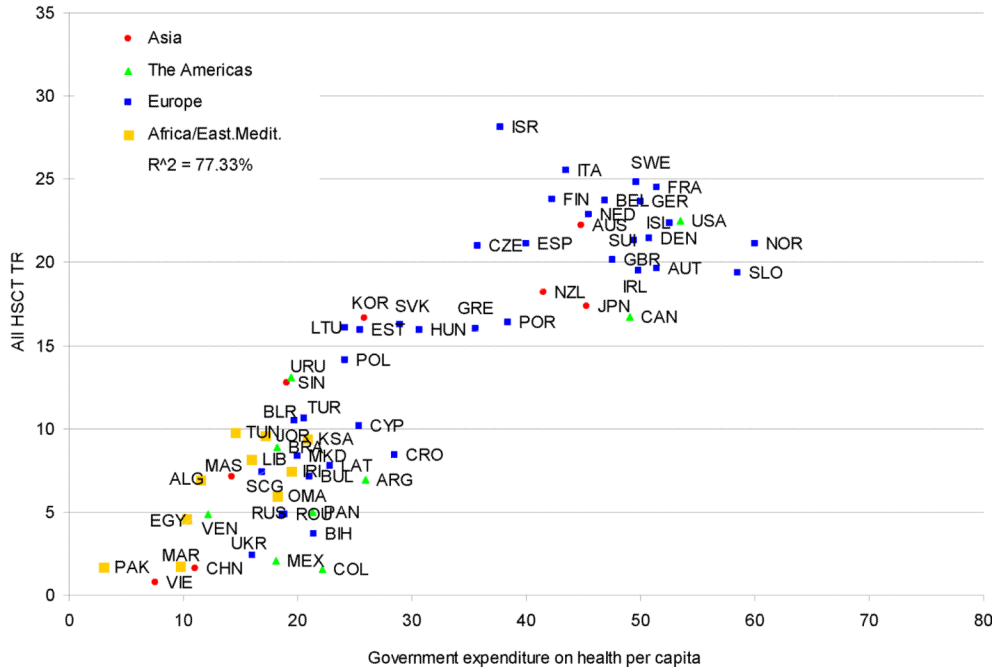


Figure 3b

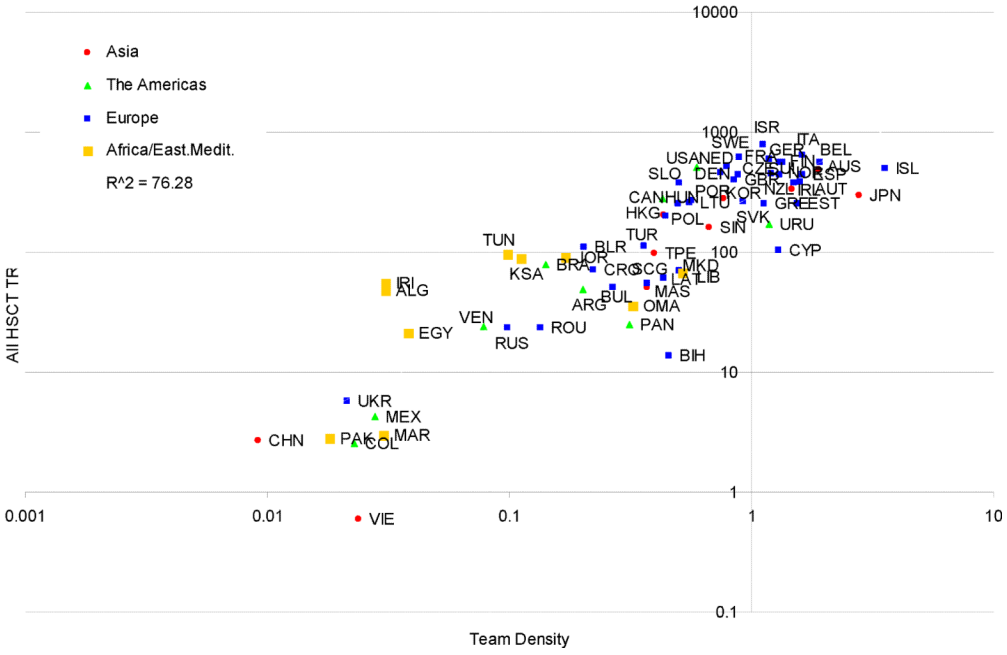

Figure 3c

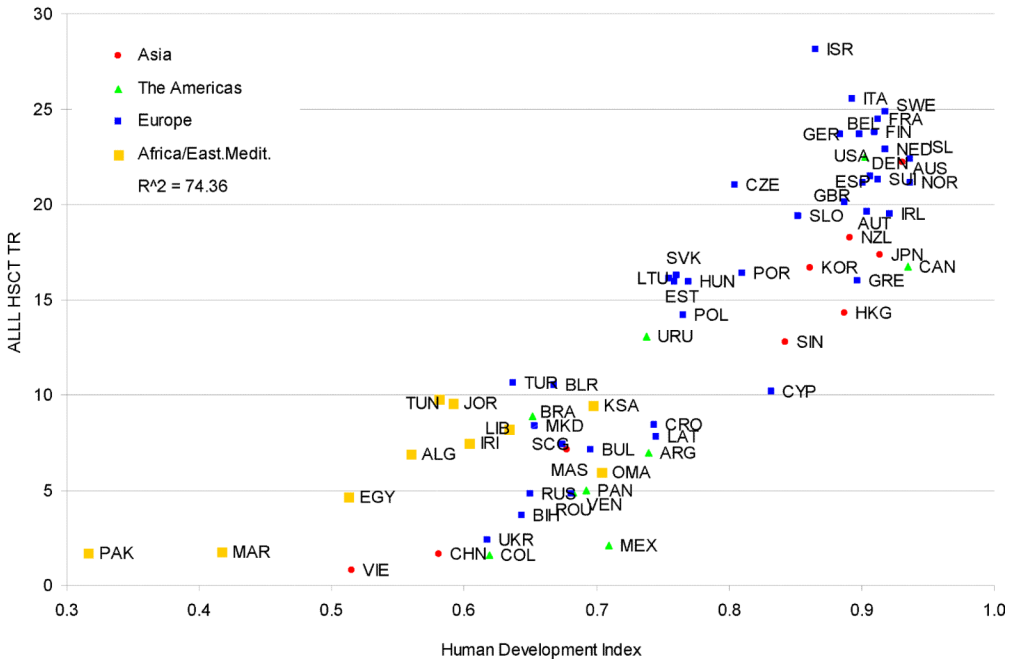


**Fig 3. Macro-economic factors and transplant rates**

Dots represent individual countries. Country code according to the Olympic committee country code (http://www.olympia-statistik.de/ABC.htm).

Colors represent regions. Blue: America; green: Europe; magenta: Asia; yellow: EMRO/ Africa

**a** Transplant rates and Governmental Health Care Expenditures

**b** Transplant rates and team density

**c** Transplant rates and Human Developmental Index

## Table 1

Numbers of transplant teams and hematopoietic stem cell transplants world-wide in 2006 by donor type.

| Teams = 1327 | Family | Allogeneic Unrelated | Total | Autologous | Total |
|---|---|---|---|---|---|
| **Leukemia's** | **8122** | **7088** | **15210** | **1839** | **17049** |
| Acute myeloid leukemia | 3907 | 3119 | 7026 | 1372 | 8398 |
| Acute lymphoblastic leukemia | 1799 | 1850 | 3649 | 216 | 3865 |
| Chronic myeloid leukemia | 877 | 519 | 1396 | 14 | 1410 |
| Myelodysplastic, myeloproliferative syndromes | 1151 | 1248 | 2399 | 60 | 2459 |
| Chronic lymphocytic leukemia | 336 | 269 | 605 | 175 | 780 |
| Other leukemia | 52 | 83 | 135 | 2 | 137 |
| **Lymphoproliferative disorders** | **2088** | **1414** | **3502** | **23990** | **27492** |
| Plasma cell disorders | 546 | 287 | 833 | 11877 | 12710 |
| Hodgkin's disease | 270 | 235 | 505 | 3275 | 3780 |
| Non Hodgkin's lymphoma | 1109 | 708 | 1817 | 7943 | 9760 |
| Other lymphoma/Type unknown | 163 | 184 | 347 | 895 | 1242 |
| **Solid tumors** | **113** | **40** | **153** | **2772** | **2925** |
| Neuroblastoma | 22 | 8 | 30 | 615 | 645 |
| Germinal cancer | 3 | 2 | 5 | 518 | 523 |
| Breast cancer | 13 | 4 | 17 | 273 | 290 |
| Ewing's sarcoma | 17 | 6 | 23 | 176 | 199 |
| All others | 58 | 20 | 78 | 1190 | 1268 |
| **Non malignant disorders** | **1512** | **884** | **2396** | **197** | **2593** |
| Bone marrow failures | 879 | 457 | 1336 | 0 | 1336 |
| Hemoglobinopathies | 348 | 54 | 402 | 3 | 405 |
| Immune deficiencies | 216 | 241 | 457 | 3 | 460 |
| Inherited diseases of metabolism | 63 | 122 | 185 | 2 | 187 |
| Autoimmune disorders | 6 | 10 | 16 | 189 | 205 |
| **Others** | 93 | 162 | 255 | 103 | 358 |
| **TOTAL** | **11928** | **9588** | **21516** | **28901** | **50417** |

**Table 2**

Main indications for autologous and allogeneic HSCT by region

| Allogeneic | Americas | Asias | Europe | EMRO/Africa | Total |
|---|---|---|---|---|---|
| Leukemias | 5156 | 3119 | 6443 | 492 | 15210 |
| Lymphoproliferative disorders | 1466 | 429 | 1579 | 28 | 3502 |
| Solid Tumors | 32 | 37 | 83 | 1 | 153 |
| Non Malignant disorders | 755 | 418 | 946 | 277 | 2396 |
| Others | 118 | 55 | 77 | 5 | 255 |
| Total | 7527 | 4058 | 9128 | 803 | 21516 |
| Autologous | | | | | |
| Leukemias | 443 | 202 | 1136 | 58 | 1839 |
| Lymphoproliferative disorders | 8936 | 2380 | 12336 | 338 | 23990 |
| Solid Tumors | 895 | 389 | 1459 | 29 | 2772 |
| Non Malignant disorders | 49 | 23 | 123 | 2 | 197 |
| Others | 25 | 44 | 34 | 0 | 103 |
| Total | 10348 | 3038 | 15088 | 427 | 28901 |
| Total | 17875 | 7096 | 24216 | 1230 | 50417 |