

# Factors influencing CMV seropositivity in stem cell transplant patients and donors

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## ABSTRACT

CMV status of the donor and the recipient influence the outcome of allogeneic stem cell transplantation. To study factors determining CMV status, 40,311 patients and 23,048 donors were identified in the EBMT registry. Logistic regression models predicting seropositivity were constructed. Female patients were more likely to be seropositive ( $p < 0.001$ ). The risk increased with age ( $p < 0.001$ ) but decreased according to the year of transplant ( $p < 0.001$ ). There were differences in the probability of seropositivity between patients from different countries. Adjusted for patient serostatus, the risk of a donor being seropositive was higher in females ( $p < 0.001$ ) and older donors ( $p < 0.001$ ).

Key words: CMV, stem cell transplantation, serology.

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Patient MV serological status remains an important factor for the outcome of allogeneic stem cell transplantation (SCT).<sup>1-3</sup> CMV seronegative patients receiving a graft from a seronegative donor have lower transplant-related mortality.<sup>4,5</sup> In a previous study using the EBMT registry, we found that CMV seropositive patients receiving grafts from seropositive unrelated donors had improved survival and reduced transplant-related mortality compared to those receiving grafts from CMV seronegative donors.<sup>6</sup> Similar results were found in a single centre study by Ringdén *et al.*<sup>7</sup> However, two other large studies have not been able to show any positive effect from using a CMV seropositive donor.<sup>1,8</sup>

Many different factors influence the risk of being CMV seropositive. The probability varies between different countries. One study suggests that the risk has been reduced in recent years.<sup>9</sup> We used the registry of the European Group for Blood and Marrow Transplantation (EBMT) to look for trends over time regarding CMV serostatus and analyze the effects of age, gender and country.

## Design and Methods

The EBMT registry was set up in the mid 1980s. It is obligatory for EBMT members

to report a core data set, the so called MED-A data set. In this the CMV serological status of both patients and, if applicable, of the stem cell donors are included.

### Patients

Included in these studies were 40,311 patients whose pre-transplant CMV serological status was known from transplants performed in the period 1985-2004. Of these, 31,198 patients underwent an allogeneic SCT and 9108 underwent an autologous SCT. Patient nationality was assumed to be that of the country where the transplant was performed.

### Donors

Included in the study were 23,048 donors whose CMV serological status was known. Since it is well known that the use of a CMV seronegative donor to a seronegative patient is favorable, there might be a selection bias in favor of seronegative donors in the registry. Therefore, we performed a separate analysis including only donors to CMV seropositive patients and 18,873 donors were identified for the subset analysis.

### CMV serology

Patients and donors had their serological status determined at their local laboratory.

Different techniques with different cut-offs for seropositivity were therefore used.

**Statistics**

Logistic regression models predicting seropositivity were constructed using the year of SCT, age, gender and country as fixed covariates. When donor seropositivity was modeled, age and gender were those of the donors. When modeling patient seropositivity, the age, gender and country of the patient were used. In all models, the above mentioned variables were entered simultaneously into the model to assess their simultaneous influence on the outcome. To examine whether influences on seropositivity might differ between subgroups defined by the main predictors, an interaction term was added to the model and the likelihood ratio test was used to test for effect modification. *p* values <0.05 were considered to be significant. A threshold of 0.10 was used for interactions.

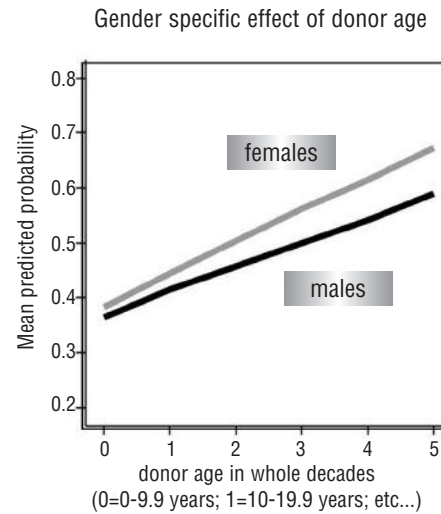
**Results and Discussion**

**Serological status of donors**

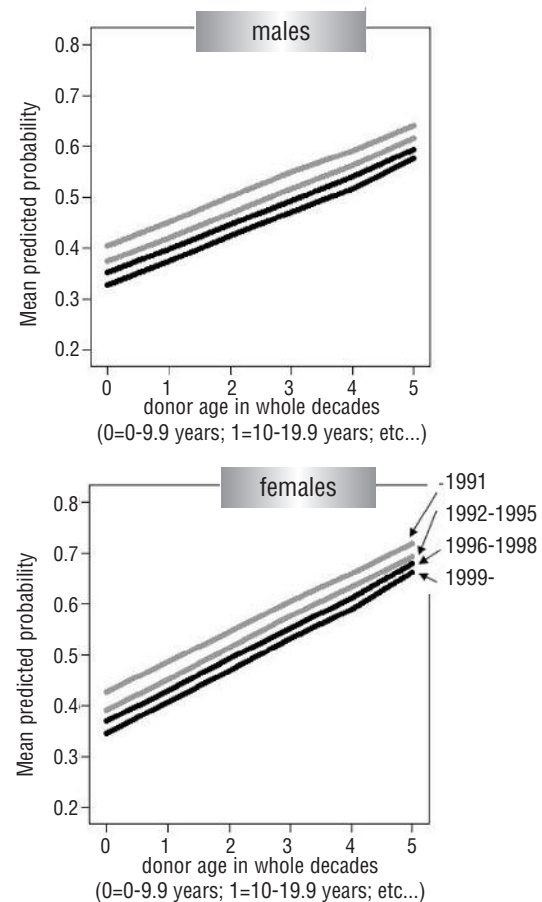
The mean age of the donors was 33.5 years (males: 33.8 years, SD 14.7; females: 33.3 years, SD 15.4). There were 12,835 (55.6%) male donors and 10,213 (44.4%) female. Among all donors, 11,948 (51.8%) were CMV seropositive and 11,070 (48.2%) seronegative. In multivariate logistic regression analysis adjusted for patient serostatus as a main factor, the risk of seropositivity increased with female gender (OR 1.29; 1.22-1.37; *p*<0.001) and increasing age (OR 1.24/decade; 1.21-1.27; *p*<0.001). The predicted probability increased at a stable rate in both females and males (Figure 1). Furthermore, the risk decreased by the calendar year of transplant (0.98/year; 0.97-0.98; *p*<0.001; Figure 2). In the separate analysis including only donors to CMV seropositive patients (n=18,873), there was a slightly higher proportion of CMV seropositive donors (54.7%) compared to the whole cohort. The results were otherwise similar with an increased risk for females and increasing age but a decreased risk for donors registered more recently in the database (*data not shown*).

**Serological status of patients**

The mean age of the patients was 31.0 years (males: 30.9 years, SD 16.4; females; 31.1 years, SD 16.1). There were 23,505 (58.3%) male patients and 16,806 (41.7%) female. Among all patients, 21,742 (53.9%) were seropositive and 18,569 (46.1%) seronegative. Female patients had a higher likelihood of being seropositive than males (OR 1.22; 1.15-1.30; *p*<0.001). The risk of being seropositive increased by age (OR 1.19/decade; 1.17-1.21; *p*<0.001) but decreased according to the calendar year of transplant (OR 0.98/year, 0.97-0.99; *p*<0.001).



**Figure 1.** Donor positivity as a function of gender and age.



**Figure 2.** Donor Donor positivity as a function of age over calendar year periods. Separate for donor gender.

There were major differences between patients transplanted in different countries with patients from France, Germany, Belgium and the Netherlands having the low-

**Table 1.** Estimated probability of CMV seropositivity in stem cell transplant patients for the year 2000 according to country.

Country	
1 Netherlands+Belgium	0.51
2 France	0.56
3 Spain	0.74
4 Italy	0.88
5 United Kingdom	0.54
6 Nordic	0.74
7 Germany	0.56
<b>Average</b>	<b>0.62</b>

est and Italy the highest probability of being CMV seropositive. The mean age was the highest for the German patients (35.5 years) and the lowest for the UK patients (28.0). The estimated probability of patient seropositivity for the year 2000 for different countries is shown in Table 1. The probability of seropositivity among patients after correction for patient age and gender was seen to be significantly decreasing over time in France, Italy and the UK. There were no significant trends for the other countries studied.

CMV has a high seroprevalence in the population. There are several possible routes for CMV transmission<sup>10-13</sup> resulting in natural variations in prevalence depending on gender, parity and age. Also socio-economic factors can influence the risk.<sup>14</sup> Geographical location also influences risk with different seroprevalences in different countries<sup>15,16</sup> and variations within a country.<sup>17</sup> Our large sample size allowed an analysis of risk factors for CMV seropositivity and of trends over time given that the cohort was collected over approximately 20 years.

As expected, we found that the probability of being seropositive increased with age in both men and women. The risk increased at a constant rate in both patients and donors although the increase according to age was more pronounced in females. Ahlfors found age to have a similar effect in a study published more than 20 years ago.<sup>15</sup> In a recent report, Staras *et al.* found risk increased with age and that there was a higher risk in females similar to our results.<sup>18</sup> It is interesting that the probabilities of being seropositive has been decreasing over time in both men and women and in all age groups. The reasons are unknown. Similar results have been obtained in a study of females aged 2-40 in Madrid, Spain.<sup>9</sup> These authors found a statistically significant reduction in seroprevalence among girls aged 6-10 and women aged 31-40 years.

We found large variations in the predicted probabilities of a 40 year old male patient being seropositive between different European countries. In general terms,

the seroprevalence was higher in southern than in northern Europe except in Nordic countries where the seroprevalence was similar to that of southern Europe. The reason for this is unknown but one possibility is that day care centers were introduced early in the Nordic countries. There was no interaction between patient gender and country. Therefore, data show that the effect of geographical location was maintained across male and female patients. Furthermore, when corrected for age and gender, the probability of being seropositive decreased significantly over time in France, Italy, and the UK but not in the other countries studied. The reasons for these different trends are unknown and merit further study but possible explanations could include decreasing birth rates and a delay in childbearing until an older age. Of course, patients undergoing SCT form a very special group and therefore results might not be applicable to a healthy population. Two possible biases were identified; the selection of seronegative donors to seronegative patients and that unrelated donors did not always come from Europe. However, apart from these reservations, our study showed that the same trends with decreasing probability over time and geographical variations (*data not shown*) were seen in the donors.

Since one way of transmission of CMV is via blood transfusion, and given that this study also included a period before the introduction of routine screening practices of blood donors or widespread use of leukocyte depleted blood products, it would be interesting to see how much impact blood transfusions had on the overall risk of CMV seropositivity. Overall, patients were slightly more likely to be CMV seropositive than donors (53.9% vs. 51.0%). Two factors were significantly associated with a lower risk for CMV seropositivity: patients were slightly younger (31 vs. 33.5%) and a lower proportion was female (41.7% vs. 44.4%). Due to the selection bias in choosing seronegative donors for seronegative patients, it is difficult to perform a meaningful statistical analysis. However, it seems likely that blood transfusions did influence the comparison between the patient and the donor cohorts.

We conclude that the likelihood of being CMV seropositive is higher in females and older individuals. There are strong differences in the probability of being seropositive between patients transplanted in different countries. Trends over time also differ between countries.

#### Authors' Contributions

PL designed the study and wrote the paper; RB performed the statistical analysis and reviewed the paper

#### Conflicts of interest

The authors reported no potential conflicts of interest.

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