SURVIVAL AFTER BLOOD TRANSFUSION

Mads Kamper-Jørgensen[1], Martin Ahlgren[1], Klaus Rostgaard[1], Mads Melbye[1], Gustaf Edgren[2], Olof Nyrén[2], Marie Reilly[2], Rut Norda[3], Kjell Titlestad[4], Elsa Tynell[5], Henrik Hjalgrim[1]

[1]Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark

[2]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

[3]Department of Immunology and Transfusion Medicine, Uppsala University Hospital, Uppsala, Sweden

[4]Department of Clinical Immunology, Odense University Hospital, Odense, Denmark

[5]Department of Medicine, Infectious Diseases Unit, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden

Word count, text only: 3,404

Word count, abstract: 222

Correspondence to Dr. Mads Kamper-Jørgensen, Statens Serum Institut, Department of Epidemiology Research, Artillerivej 5, 2300 Copenhagen S, Denmark. Telephone: +45 32688339, Fax: +45 32683165, E-mail: mka@ssi.dk

Funding: The present study was supported by the National Institutes of Health, National Heart Lung and Blood Institute, the Danish Medical Research Counsel (FSS) and Aase and Ejnar Danielsen's Foundation.

The definitive version is available at www.blackwell-synergy.com.

Running head: Survival after blood transfusion

Abstract

Background

Long-term survival of transfusion recipients has rarely been studied. We examined short- and long-term mortality among transfusion recipients, and reported these as absolute rates and rates relative to the general population.

Study design and methods

Population-based cohort study of transfusion recipients in Denmark and Sweden followed for up to 20 years after their first blood transfusion. Main outcome measure was all-cause mortality.

Results

We identified 1,118,261 transfusion recipients of whom 62.0% were aged 65 years or older at the time of their first registered transfusion. Three months after the first transfusion, 84.3% of recipients were alive. One-, five- and twenty-year post-transfusion survival was 73.7%, 53.4% and 27.0%, respectively. Survival was slightly poorer in men than in women, decreased with increasing age, and was worst for recipients transfused at departments of internal medicine. The first three months after the first transfusion, the standardized mortality ratio (SMR) was 17.6 times higher in transfusion recipients than in the general population. One to four years after first transfusion, the SMR was 2.1 and even after 17 years the SMR remained statistically significantly 1.3-fold increased.

Conclusion

We characterized survival and relative mortality patterns among blood transfusion recipients with unprecedented detail and precision. Our results are relevant to assessments of the consequences of possible transfusion-transmitted disease as well as for cost-benefit estimation of new blood safety interventions.

Key words

Transfusion, survival, mortality, Scandinavia, Denmark, Sweden.

Introduction

Information on survival patterns of transfusion recipients is essential for the continued assessment of transfusion-transmitted diseases and thus to the implementation of new and often expensive screening techniques[1-4]. However, long-term survival of transfusion recipients has only been sparsely studied and accordingly remains poorly characterized. The largest study to date reported cumulative survival estimates and crude mortality rates for 6,779 recipients in the period up to five years after the transfusion event[5]. To our knowledge, information on longer follow-up, seven and ten years, is available only from two smaller cohorts of 932 and 802 transfusion recipients, respectively[6,7]. The need for precise information is emphasized by suggested secular trends in recipient survival[6,7] and by the realization that some transfusion-related complications possibly become manifest only decades after the transfusion event, e.g. variant Creutzfelt Jacob's disease[8].

In the absence of reliable or sufficiently detailed survival data, estimates of cost-effectiveness of proposed screening techniques often rely on crude assumptions about transfused patients' mortality, e.g. a constant mortality probability more than three years after transfusion[9]or a mortality that would resemble that of the general population five years after transfusion[10]. While the underlying conditions necessitating blood transfusion in the recipient make this latter assumption unlikely, comparisons of transfusion recipients' mortality rates with those prevailing in the general population are scarcely available in the literature, neither overall nor with respect to specific causes[8,11].

We assessed both absolute and relative mortality after transfusion using a Danish-Swedish population-based register encompassing more than 1.1 million transfusion recipients that were followed for up to 20 years after their first recorded blood transfusion.

Material

In Sweden and Denmark blood banks are part of the hospitals they serve, and thus they are a part of the public health care sector. Blood banks register the identity of all blood donors, all blood donations and all blood components issued to patients, as well as the identity of all recipients. In both Sweden and Denmark, computerized systems to record this information have been used in an increasing number of blood banks since the late 1960s, with complete national coverage achieved by 1996 in Sweden and 2002 in Denmark[12]. As part of the Scandinavian Donation and Transfusion (SCANDAT) database project, we collected all electronic information on donors and recipients available from Swedish and Danish blood banks. Whereas data was available for the entire period since 1966 in Sweden, Danish data was available only since 1982 because early computer systems were based on reusable tapes[12].

Since 1947 and 1968 respectively, all residents in Sweden and Denmark, have been assigned unique national registration numbers (NRN). All national registers containing identifiable information are based on the NRN, which thus serves as a unique key for register-based linkage studies. For all persons recorded in the SCANDAT database, we used Swedish and Danish population registers[13,14] to obtain vital status as of 31 December 2002, and if applicable, the date of death or emigration. Analogously, information about causes of death was obtained from the national cause of death registers[15,16]. Also as part of the SCANDAT project, information about hospitalizations, including department and primary and secondary discharge diagnoses, coded according to the International Classification of Diseases (ICD)[17], versions 6 through 10, and surgical and other procedures, were obtained for all individuals in the database through linking with the Danish and Swedish nationwide hospital discharge registers[18,19]. The creation of the SCANDAT database and the conduct of the present study were approved by appropriate scientific ethical committees and data protection agencies in both countries.

Mortality data for the general Danish and Swedish populations according to country, sex, age and calendar period was obtained from the World Health Organization[20].

Methods

Follow-up

For technical reasons relating to the initiation of computerization and to optimize comparability between Denmark and Sweden, information on recipients whose first transfusion was prior to 1 January 1983 was disregarded in both countries. Follow-up of the recipients started on the day of the first registered transfusion of any blood component and ended on the day of death, emigration or 31 December 2002, whichever came first. In the present study, a blood transfusion was defined as transfusion of one blood component emanating from one or more donors. A transfusion episode constituted a period of transfusions, separated from previous or subsequent transfusions by intervals of at least seven days of no transfusion activity[21]. Blood components included red blood cells (RBCs), fresh frozen plasma (FFP), platelets, and unknown or other components. For reasons of register completeness follow-up ended in 2000 in analyses of cause-of-death-specific and relative mortality.

Statistical analyses

Cumulative survival according to time since first transfusion was estimated by Kaplan-Meier methodology using the LIFETEST procedure in SAS v. 9.1[22]. Cumulative survival was estimated overall for the entire cohort of transfusion recipients and stratified by country, sex, age at first transfusion (0-19, 20-39, 40-64, 65-79, 80+ years), calendar period at first transfusion (1983-87, 1988-92, 1993-97, 1998-02), department of first transfusion (internal medicine, surgery, gynecology and obstetrics, other and unclassifiable, unknown) and cumulative number of transfused units received during the first month after first transfusion (1-2, 3-4, 5-10, 11+) as a time-varying covariate. Thus, in the latter case the same person may contribute follow-up time in several strata and a death in at most one stratum. The necessary calculations were done using a home grown macro for stratification and aggregation of events and follow-up time in conjunction with a data step emulating the functionality of the LIFETEST procedure. Cumulative survival was expressed as percent. Adjusted

relative mortality assessed as incidence rate ratios were estimated by log-linear Poisson regression and associated 95% confidence limits.

We also estimated the recipients' risk of dying relative to the risk in the general Danish and Swedish populations. Specifically, the relative risk of dying was expressed as the standardized mortality ratio (SMR), where the observed number of deaths is compared to the number expected based on mortality rates in the general populations in strata defined by country, sex, 5-year age-group, and one-year calendar period. Population data were available for ages 0 to 90 years for the calendar period 1983-2000[20]. SMRs were estimated with the logarithm of the expected number of cases as offset in the GENMOD procedure in SAS. Due to the huge sample size we did not find it meaningful to conduct statistical tests for homogeneity and we chose not to present the upper and lower 95% confidence limits (which were practically indistinguishable) for the cumulative survival and SMRs presented in figures and tables. To estimate the impact of assuming, as done in previous publications, that the mortality in transfusion recipients five years post transfusion is similar to that in the general population, we calculated the percentage difference between the number of deaths observed in our cohort and the expected number of deaths in the general Danish and Swedish population five to twenty years after first recorded transfusion.

Results

Transfusion recipients

A total of 1,118,261 transfusion recipients was identified, and these received a total of 9,979,082 units during 2,172,917 transfusion episodes. Seventy two percent of all transfused components were RBCs, 19% were FFP, 7% were platelets and the remaining 2% were other components including whole blood. The first registered transfusion was autologous for 5,588 (0.5%) recipients and the donor was unknown for 60,028 (5.4%) recipients. Table 1 shows characteristics of transfusion recipients according to country and covariates. The majority of transfusion recipients (69.0%) lived in Sweden, reflecting the earlier introduction of computerized blood bank systems and a larger population. In both countries more women than men were transfused.

Median age at first transfusion was 69.9 (inter quartile range 55.3-79.4) and 70.9 (inter quartile range 56.3-79.7) in Denmark and Sweden, respectively. Age at first registered transfusion increased over time in the cohort. For calendar periods 1983-87, 1988-92, 1993-97, and 1998-02 median ages at first transfusion were 63.9, 68.2, 71.4 and 72.5 years, respectively. Overall, 62.0% of the transfused patients were 65 years or older at first transfusion.

The distribution of transfusion recipients according to calendar period at first transfusion differed between Denmark and Sweden, reflecting the introduction of computerized blood bank systems at different times. In the total cohort, 73.1% of recipients had a transfusion registered for the first time during the period 1993-2002. The majority of recipients were transfused for the first time while admitted to surgical departments, followed by departments of internal medicine, with the difference being more pronounced in Sweden (Table 1).

Cumulative survival

Cumulative survival by time since first transfusion stratified by covariates is shown in Table 2. Overall, 84.3% (95% CI 84.2%-84.3%) of transfusion recipients were alive three months after their first transfusion, while 73.7% (95% CI 73.6%-73.8%) were alive after one year. Five year survival

was 53.4% (95% CI 53.3%-53.5%) and 20 year survival 27.0% (95% CI 26.8%-27.2%). At all times after first transfusion, Danish recipients had poorer survival than Swedish recipients, which persisted even after adjustment for calendar period, age, sex department of first transfusion and cumulative number of units received (data not shown). Also, men had poorer survival than women. Cumulative survival also varied by department of first transfusion. Women transfused at departments of gynecology and obstetrics had the best survival, whereas patients transfused at departments of internal medicine had the worst. Poorer survival among Danish recipients was observed at all types of departments (data not shown). At all times since first transfusion, survival was negatively associated with increasing number of units received during the first month after first transfusion. Twenty years after first transfusion only 19.3% (95% CI 18.7%-19.9%) of those who received 11 units or more were alive compared with 31.5% (95% CI 31.2%-31.8%) of those who received only 1-2 units.

As illustrated in Figure 1 showing cumulative survival by time since first transfusion for different age groups, increasing age at first transfusion was associated with worse survival, with the exception of recipients aged 0-19 years who had slightly worse survival than recipients aged 20-39 years. One year survival was 92.1% (95% CI 91.9%-92.4%) in 0-19-year-olds, 93.6% (95% CI 93.5%-93.8%) in 20-39-year-olds, 78.6% (95% CI 78.4%-78.7%) in 40-64-year-olds, 71.9% (95% CI 71.7%-72.0%) in 65-79-year-olds and 61.3% (95% CI 61.1%-61.5%) in recipients aged 80 years or more.

Figure 2 shows that absolute survival decreased by calendar period of first transfusion. Among recipients transfused in 1983-87, one-year survival was 79.1% (95% CI 78.9%-79.4%). Corresponding figures for 1988-92, 1993-97 and 1998-02 were 75.2% (95% CI 75.0%-75.4%), 73.3% (95% CI 73.1%-73.4%) and 72.1% (95% CI 72.0%-72.3%), respectively. Analysis of survival for different calendar periods revealed that when adjusted for time since first transfusion, age, sex, country, department of first transfusion and cumulative number of units received, there were no significant differences between the different calendar periods (data not shown).

Relative mortality

The standardized mortality ratio (SMR) of transfusion recipients relative to the general population by time after first transfusion and covariates are shown in Table 3. Overall, the standardized mortality ratio was 17.6 (95% CI 17.5-17.7) times higher in the transfused cohort during the first three months after first transfusion, meaning that during the first three months after first transfusion recipients had a 17.6 times higher risk of dying compared with a person in the general population with similar demographic characteristics i.e. from the same country, of same age and sex and during the same calendar period. The SMR was 2.1 (95% CI 2.1-2.1) in the period from 1 to 4 years after first transfusion, and even 15-17 years after first transfusion a statistically significantly increased SMR of 1.3 (95% CI 1.2-1.4) persisted. The relative mortality of transfusion recipients was slightly higher in Denmark than in Sweden for the first ten years after first transfusion, and slightly higher for men than for women.

Irrespective of the type of department at which the first transfusion was given, the relative risk of dying was the highest shortly after transfusion. With continued follow-up patients transfused at departments of internal medicine continued to have the highest relative risk of dying, whereas women transfused at departments of gynecology and obstetrics had only a slightly increased risk of dying 10 years or more after the transfusion event. Increasing number of units received during the first month after first transfusion was associated with increasing mortality relative to the general population. While being most pronounced shortly after first transfusion, this was true at all times since first transfusion. Cause-of-death-specific SMRs showed that the increased relative mortality applied to all causes of death, and were highest for digestive, neoplastic, and infectious diseases.

Figure 3 shows SMRs according to time since first transfusion for different age groups. During the first years following a transfusion, the SMR was markedly increased for all age groups, though most for the youngest age groups. Even after more than 15 years of follow-up an excess

mortality was observed in transfusion recipients; the younger the recipient was at time of first transfusion the higher the persistent excess mortality.

As illustrated in Figure 4, the decrease in excess SMR of transfusion recipients following a transfusion was comparable in recipients transfused in different calendar periods. Assuming the mortality pattern in transfusion recipients five years post transfusion is similar to that of the general population, we underestimated the number of deaths by 33%.

Discussion

In the present study we took advantage of information about more than 1.1 million transfusion recipients registered in databases in Swedish and Danish blood banks in the calendar period between 1983 and 2002. Combined with data from nationwide population and cause-of-death registers, we were able to characterize patterns of both absolute and relative survival after transfusion with unprecedented precision.

Although practically and ethically challenging to study, it has been suggested that blood transfusion in itself may increase the risk of death in critically ill patients[23]. While the design of our study did not allow us to investigate this, we believe that the poor survival following blood transfusion demonstrated in the present study reflects that transfusions are given to patients who already are at increased risk of dying from e.g. trauma, major operations or serious illness.

Consistent with previous studies, absolute mortality was high in the period shortly after blood transfusion. The excess relative mortality among transfusion recipients was not restricted to the period shortly after first transfusion, but was apparent even 17 years after first transfusion. As in previous studies, determinants of a decreased absolute survival included male sex, and old age [6-8,11,24]. Although survival is also lower in men than in women in the general population, the relative measure of mortality revealed that the excess mortality among transfusion recipients was more pronounced in men than in women. Despite decreasing absolute survival with increasing age, mortality among transfusion recipients relative to the general population was highest in the youngest age group. As also suggested in earlier surveys[5-8,11,24], the absolute survival of transfusion recipients decreased in more recent calendar periods. This is likely to in part reflect the increasing age of the recipients since we observed no differences between different calendar periods after adjusting for age, sex and country. Accordingly, we found no indication that survival among transfusion recipients decreased in more recent periods.

In addition to old age, male sex, and recent calendar period transfusion recipients' mortality was also influenced by the condition necessitating blood transfusion and by the number of units re-

ceived. Using department at first transfusion as a crude proxy measure of indication, patients admitted to departments of internal medicine had the highest mortality, both absolute and relative to the general population. Similarly, patients receiving most transfusions were at highest risk of dying. On both absolute and relative scales, the lowest mortality was observed among women receiving transfusions at obstetrical and gynecological departments. Absolute mortality was high due to cardiovascular and neoplastic diseases and low due to infectious, respiratory and digestive diseases. However, relative to the general population mortality due to infectious and digestive diseases was markedly elevated in transfusion recipients. As expected, relative mortality was also markedly increased for neoplastic diseases. This observed variation in absolute mortality is consistent with previous findings[6-8,11,24].

A higher absolute mortality in Denmark compared with Sweden is a general phenomenon, not limited to transfusion recipients. Generally, the higher absolute mortality in Denmark is ascribed to a higher level of tobacco smoking and alcohol consumption[25]. SMRs stratified by country showed marginally lower SMRs in Swedish recipients than in Danish recipients. This difference is not readily explained, but presumably is not related to more strict transfusion criteria in Denmark, as more transfusions are administered in Denmark than in Sweden relative to the population size[12]. Adjusted analyses revealed that the higher mortality in Denmark could not be attributed to differences in calendar period, age, sex, department of first transfusion or cumulative number of units received.

Absolute survival estimates more than 10 years after first blood transfusion have not previously been available, nor have comparisons with expected mortality to any greater extent[8,11]. The most important finding presented in this regard is the substantial long-term survival indicating that even transfusion-transmitted diseases with very long incubation periods can potentially affect a considerable number of individuals[26]. Overall, our analyses also revealed that the recipients continued to have a 30% increased mortality relative to the general population 15-17 years after first transfusion. On the other hand, transfusion-transmitted infectious agents would accumulate in patients receiving

multiple transfusions and the long-term survival of these patients is as shown in the present analyses markedly lower than other recipients' survival. Accordingly, both estimates of long-term survival of transfusion recipients and the uneven distribution by number of transfused units should ideally be factored in future policy decisions and cost-effectiveness calculations.

A number of factors related to blood transfusion therapy vary both between and within countries and over time[27]. This includes blood product manufacturing procedures, treatment regimes, private/public health care system, and blood transfusion policies. Even within countries, different indications for transfusion likely exist in different hospitals for the same patient categories[28]. Furthermore, transfusion criteria have likely changed over time in individual hospitals, e.g. as a result of the Human Immunodeficiency Virus (HIV) epidemic. Accordingly, the higher age of recipients transfused in later calendar periods in our study may reflect more strict transfusion criteria after the onset of the HIV epidemic and/or more aggressive treatment even in elderly patients. Our findings therefore highlight the need for caution in making direct comparisons of absolute survival between studies.

Our population-based cohort was very large, as it comprised all transfusion recipients in Denmark and Sweden from 1 January 1983 for whom computerized transfusion records existed. Because of the continuously updated civil registration systems in both countries, there was virtually no loss to follow-up. However, nationwide or near nationwide coverage was not achieved until the late 1990's in the two countries. It is possible therefore, that some recipients, especially in the older age groups, were transfused prior to inclusion in the current cohort and thus have had a longer survival than we have estimated. We could, on the other hand, also have missed some transfusion recipients altogether if they had died before inclusion, and this would result in an increased proportion of "survivors" in the early cohort. The differences in the Danish and Swedish part of the data regarding the distribution of departments of first transfusion are also affected by the gradually increasing national

coverage in the two countries. Transfusion of whole blood was administered in Denmark and Sweden until the beginning of the 1980s, at which time blood component therapy was introduced.

We had access to detailed mortality rates for the general populations, and could therefore produce standardized mortality ratios in addition to absolute survival estimates. In theory, our estimates would be biased towards unity, i.e. be conservative, as the available background mortality rates are based on the total population, which includes deaths in transfusion recipients. Finally, it must be emphasized that no analyses were performed of the indication for transfusion, and that we did not intend to study the possible effects of blood transfusion itself on survival. Had the scope of our study been etiologic rather than descriptive, a group of patients with similar characteristics who did not receive transfusion would be a more suitable group for comparison than the general population.

In conclusion, our study contributes new information on both short and long-term survival of transfusion recipients. Our results provide information to improve assessments of the consequences of possible transfusion-transmitted disease, as well as estimates of cost-benefit of new screening techniques. Furthermore, our work emphasises that any comparisons of survival of recipients between studies requires in-depth knowledge of the composition of the transfusion recipient cohorts.

Acknowledgements

The present study was supported by the National Institutes of Health, National Heart Lung and Blood Institute, the Danish Medical Research Counsel (FSS) and Aase and Ejnar Danielsens Foundation.

Table 1. Characteristics of transfusion recipients according to country and covariates.

	Denmark	Sweden	Total cohort
Total, N (row %)	346,071 (31.0%)	772,190 (69.0%)	1,118,261 (100%)
Sex, N (col%)			
Men	155,502 (44.9%)	344,868 (44.7%)	500,370 (44.8%)
Women	190,569 (55.1%)	427,322 (55.3%)	617,891 (55.2%)
Age at first transfusion, N (col%)			
0-19 yr	11,814 (3.4%)	27,299 (3.5%)	39,113 (3.5%)
20-39 yr	28,945 (8.4%)	70,050 (9.1%)	98,995 (8.9%)
40-64 yr	96,279 (27.8%)	190,309 (24.7%)	286,588 (25.6%)
65-79 yr	127,901 (37.0%)	297,896 (38.6%)	425,797 (38.1%)
80+ yr	81,132 (23.4%)	186,636 (24.1%)	267,768 (23.9%)
Period at first transfusion, N (col%)			
1983-87	19,090 (5.5%)	97,455 (12.6%)	131,663 (11.4%)
1988-92	42,194 (12.2%)	129,172 (16.7%)	178,984 (15.5%)
1993-97	106,326 (30.7%)	252,271 (32.7%)	364,474 (31.7%)
1998-02	178,461 (51.6%)	293,292 (38.0 %)	476,553 (41.4%)
Department of first transfusion, N (col%)			
Surgery	173,488 (50.1%)	478,380 (62.0%)	651,868 (58.3%)
Internal medicine	124,884 (36.1%)	176,508 (22.9%)	301,392 (27.0%)
Gynecology and obstetrics	19,058 (5.5%)	56,242 (7.2%)	75,300 (6.7%)
Other and unclassifiable	2,191 (0.6%)	5,492 (0.7%)	7,683 (0.7%)
Unknown	26,450 (7.7%)	55,568 (7.2%)	82,018 (7.3%)

Table 2. Cumulative survival (%) after first transfusion according to time since first transfusion and covariates.

	---------- Time since first transfusion ----------						
	3 mo	**6 mo**	**1 yr**	**5 yr**	**10 yr**	**15 yr**	**20 yr**
Overall	84.3	79.5	73.7	53.4	40.3	32.2	27.0
Country							
Denmark	80.6	75.2	68.8	47.5	35.0	27.5	22.6
Sweden	85.9	81.4	75.9	55.9	42.5	34.1	28.6
Sex							
Men	81.6	76.2	69.9	49.5	36.3	27.5	21.9
Women	86.5	82.1	76.9	56.5	43.6	36.2	31.2
Department of first transfusion							
Surgery	87.0	83.2	78.3	57.7	42.1	31.7	24.6
Internal medicine	74.8	67.6	59.3	35.5	24.4	18.8	15.1
Gyn. and obstetrics	96.5	95.1	93.0	86.2	83.2	80.8	78.1
Other and unclassifiable	78.7	73.5	67.1	42.5	26.8	20.9	18.2
Unknown	86.1	79.8	72.7	52.9	41.1	33.9	29.3
Number of units*							
1-2	87.1	82.3	76.6	55.8	43.0	35.8	31.5
3-4	84.7	79.6	73.5	52.0	38.4	29.9	24.5
5-10	80.6	75.7	70.2	50.6	37.2	28.4	22.2
11+	68.1	64.4	59.9	45.1	34.0	25.6	19.3

*Cumulative number of units received during the first month after first transfusion estimated as a time-varying covariate

Table 3. Standardized mortality ratio (SMR) of transfusion recipients relative to the general population, according to time since first transfusion and covariates.

	---------- Time since first transfusion ----------						
	0-2 mo	**3-5 mo**	**6-11 mo**	**1-4 yr**	**5-9 yr**	**10-14 yr**	**15-17 yr**
Overall	17.6	6.0	3.9	2.1	1.5	1.4	1.3
Country							
Denmark	21.0	6.7	4.4	2.4	1.6	1.4	1.4
Sweden	16.2	5.7	3.8	2.0	1.5	1.4	1.3
Sex							
Men	19.1	6.3	4.1	2.1	1.5	1.4	1.3
Women	16.1	5.7	3.8	2.1	1.5	1.4	1.3
Department of first transfusion							
Surgery	12.9	4.2	2.8	1.7	1.4	1.4	1.3
Internal medicine	29.6	10.2	6.8	3.6	2.4	2.1	1.7
Gyn. and obstetrics	22.0	10.2	8.3	4.1	1.5	1.1	1.2
Other and unclassifiable	18.8	5.0	3.5	2.2	2.4	1.7	1.0
Unknown	16.8	8.5	5.3	2.3	1.4	1.3	1.3
Number of units*							
1-2	14.2	5.5	3.7	2.1	1.5	1.3	1.1
3-4	15.4	6.0	3.9	2.1	1.5	1.4	1.3
5-10	20.6	6.4	4.1	2.1	1.6	1.5	1.4
11+	48.7	8.5	5.5	2.6	1.8	1.7	1.7
Cause of death							
Infectious disease	31.5	6.3	3.7	2.2	1.7	1.5	1.7
Neoplastic disease	36.3	17.0	10.7	3.8	1.6	1.4	1.2
Cardiovascular disease	9.0	2.5	1.7	1.5	1.4	1.4	1.4
Respiratory disease	8.7	2.4	1.9	1.5	1.4	1.2	1.1
Digestive disease	49.9	6.3	3.9	2.7	2.1	1.8	1.3
Other diseases	17.0	3.9	2.7	2.0	1.6	1.5	1.2

*Cumulative number of units received during the first month after first transfusion estimated as a time-varying covariate

Figure legends

Figure 1. Cumulative survival (%) according to time since first transfusion and age at first transfusion

Figure 2. Cumulative survival (%) according to time since first transfusion and calendar period at first transfusion

Figure 3. Survival of transfusion recipients relative to the general population (SMR) according to age at first transfusion

Figure 4. Survival of transfusion recipients relative to the general population (SMR) according to calendar period at first transfusion

References

1. AuBuchon JP, Birkmeyer JD, Busch MP. Cost-effectiveness of expanded human immunodeficiency virus-testing protocols for donated blood. Transfusion 1997 Jan;37(1):45-51.

2. Busch MP, Dodd RY, Lackritz EM, AuBuchon JP, Birkmeyer JD, Petersen LR. Value and cost-effectiveness of screening blood donors for antibody to hepatitis B core antigen as a way of detecting window-phase human immunodeficiency virus type 1 infections. The HIV Blood Donor Study Group. Transfusion 1997 Oct;37(10):1003-11.

3. Marshall DA, Kleinman SH, Wong JB, AuBuchon JP, Grima DT, Kulin NA, Weinstein MC. Cost-effectiveness of nucleic acid test screening of volunteer blood donations for hepatitis B, hepatitis C and human immunodeficiency virus in the United States. Vox Sang. 2004 Jan;86(1):28-40.

4. Tynell E, Andersson S, Lithander E, Arneborn M, Blomberg J, Hansson HB, Krook A, Nomberg M, Ramstedt K, Shanwell A, et al. Screening for human T cell leukaemia/lymphoma virus among blood donors in Sweden: cost effectiveness analysis. BMJ 1998 May 9;316(7142):1417-22.

5. Kleinman S, Marshall D, AuBuchon J, Patton M. Survival after transfusion as assessed in a large multistate US cohort. Transfusion 2004 Mar;44(3):386-90.

6. Tynell E, Norda R, Montgomery SM, Bjorkman A. Diagnosis and procedure-specific survival among transfusion of recipients in 1993 and 2000, Orebro County, Sweden. Vox Sang. 2005 Apr;88(3):181-8.

7. Vamvakas EC, Taswell HF. Long-term survival after blood transfusion. Transfusion 1994 Jun;34(6):471-7.

8. Wallis JP, Wells AW, Matthews JN, Chapman CE. Long-term survival after blood transfusion: a population based study in the North of England. Transfusion 2004 Jul;44(7):1025-32.

9. Custer B, Busch MP, Marfin AA, Petersen LR. The cost-effectiveness of screening the U.S. blood supply for West Nile virus. Ann.Intern.Med 2005 Oct 4;143(7):486-92.

10. Korves CT, Goldie SJ, Murray MB. Cost-effectiveness of alternative blood-screening strategies for West Nile Virus in the United States. PLoS.Med 2006 Feb;3(2):e21.

11. Whyte GS. The transfused population of Canterbury, New Zealand, and its mortality. Vox Sang. 1988;54(2):65-70.

12. Edgren G, Hjalgrim H, Tran TN, Rostgaard K, Shanwell A, Titlestad K, Jakobsson L, Gridley G, Wideroff L, Jersild C, et al. A population-based binational register for monitoring long-term outcome and possible disease concordance among blood donors and recipients. Vox Sang. 2006 Nov;91(4):316-23.

13. Pedersen CB, Gotzsche H, Moller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. Dan.Med.Bull. 2006 Nov;53(4):441-9.

14. Calltorp J, Adami HO, Astrom H, Fryklund L, Rossner S, Trolle Y, Giesecke J. Country profile: Sweden. Lancet 1996 Mar 2;347(9001):587-94.

15. Juel K, Helweg-Larsen K. The Danish registers of causes of death. Dan.Med.Bull. 1999 Sep;46(4):354-7.

16. The National Board of Health and Welfare. [The Swedish Cause of Death Register]. Stockholm. Report. 2005.

17. International classification of diseases. WHO Collaborating Centers. Epidemiol.Bull. 1998 Sep;19(3):7-11.

18. Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. Dan.Med.Bull. 1999 Jun;46(3):263-8.

19. The National Board of Health and Welfare. [The Swedish Inpatient Register]. Stockholm. Report. 2006.

20. WHO mortality data. Electronic citation. 2007 .

21. Reilly M, Szulkin R. Statistical analysis of donation-transfusion data with complex correlation. Stat.Med. 2007 Dec 30;26(30):5572-85.

22. SAS Institute Inc. SAS/STAT software release 9.1. Cary, NC: SAS Institute Inc. COmputer program. 2005.

23. Robinson WP, III, Ahn J, Stiffler A, Rutherford EJ, Hurd H, Zarzaur BL, Baker CC, Meyer AA, Rich PB. Blood transfusion is an independent predictor of increased mortality in nonoperatively managed blunt hepatic and splenic injuries. J.Trauma 2005 Mar;58(3):437-44.

24. Tynell E, Norda R, Shanwell A, Bjorkman A. Long-term survival in transfusion recipients in Sweden, 1993. Transfusion 2001 Feb;41(2):251-5.

25. Juel K. [Impact of tobacco, alcohol overconsumption and drug abuse on mortality in Denmark. Trends over 25 years, 1973-1997]. Ugeskr.Laeger 2001 Aug 6;163(32):4190-5.

26. Valleron AJ, Boelle PY, Will R, Cesbron JY. Estimation of epidemic size and incubation time based on age characteristics of vCJD in the United Kingdom. Science 2001 Nov 23;294(5547):1726-8.

27. Use of blood products for elective surgery in 43 European hospitals. The Sanguis Study Group. Transfus.Med. 1994 Dec;4(4):251-68.

28. Titlestad K, Georgsen J, Jorgensen J, Kristensen T. Monitoring transfusion practices at two university hospitals. Vox Sang. 2001 Jan;80(1):40-7.