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Long-term outcome after allogeneic hematopoietic cell transplantation for myelofibrosis

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Running title : long-term outcome after transplant in MF patients

ABSTRACT

Allogeneic hematopoietic stem cell transplant remains the only curative treatment for myelofibrosis. Most post-transplantation events occur during the first 2 years and hence we aimed to analyze the outcome of 2-year disease-free survivors. 1055 patients with myelofibrosis transplanted between 1995 and 2014 and registered in the registry of the European Society for Blood and Marrow Transplantation were included. Survival was compared to the matched general population to determine excess mortality and the risk factors that are associated. In the 2-year survivors, Disease-free survival was 64% (60-68%) and Overall Survival was 74% (71-78%) at 10 years, better in younger individuals and in women. Excess mortality was 14% (8-21%) in patients < 45 years and 33% (13-53%) in patients ≥ 65 years. The main cause of death was relapse of the primary disease. Graft versus Host Disease before 2 years decreased the risk of relapse. Multivariable analysis of excess mortality showed that age, male sex recipient, secondary myelofibrosis and no Graft Versus Host disease prior to the 2-year landmark increased the risk of excess mortality.

This is the largest study to date analyzing long-term outcome in patients with myelofibrosis undergoing transplant. Overall it shows a good survival in patients alive and in remission at 2-years but the occurrence of late complications, including late relapses, infectious complications and secondary malignancies highlights the importance of screening and monitoring of long-term survivors.

Key words: allogeneic hematopoietic stem cell transplantation, myelofibrosis, long-term follow-up

INTRODUCTION

Myelofibrosis (MF) is a malignant clonal disease which can be classified as either primary or secondary to either essential thrombocythemia (ET) or polycythemia Vera (PV). The clinical phenotype of MF is markedly heterogeneous and disease severity can be assessed by a number of different prognostic scoring systems. For example, utilizing Dynamic International Prognostic Scoring System "DIPSS-PLUS", low, int-1, int-2 and high-risk patients have a median survival of 15 years, 6.5 years, 35 months and 16 months, repectively[1]. JAK-2 inhibitors, specifically ruxolitinib which remains the only licensed therapeutic agent in MF, alleviate many symptoms and even possibly increase survival, are not considered curative[2–4]. Only allogeneic hematopoietic stem cells transplant (HSCT) has been proposed as curative, overall, HSCT has been reported to cure between 30 to 65% of these patients [5–16]. One registry paper analyzed the timing to transplant in patients aged <65 years and concluded that those with intermediate-2 or high-risk disease are those who clearly benefit from transplantation strategies[17]. This analysis included transplant-episodes prior to the ruxolitinib era and the role of this agent on transplantation strategies remains under debate[18]. Early mortality (within 2 years) after transplantation is known to be between 10 and 30% but to date, there is no study which has analyzed the outcome of MF transplanted patients after this early period. In contrast, long-term outcome studies have been published for HSCT recipients who have more common disease types such as acute leukemia, lymphoma and chronic myeloid leukemia[19–24]. Understanding the long-term outcome for transplanted MF patients will facilitate enhanced monitoring and an increased awareness of the potential risks of relapse or indeed mortality, specifically when compared to the general population.

METHODS

Patient selection

Only patients from countries of which the population mortality tables are available in a uniform format through the Human Mortality Database allowing a sex and age matched comparison, and contributing more than twenty allogeneic transplantations for MF were included in the study. Patients younger than 18 years and those who were transplanted from an unrelated matched cord blood were excluded. Patients were analyzed at the time of their first allogeneic transplant only. 2459 patients received a first allogeneic HCT between January 1995 and December 2014 for primary or secondary MF. A total of 1055 out of these 2459 patients were reported alive and free of their disease at 2-years after HSCT, these patients were considered for the study and called long-term (disease-free) survivors. These patients were transplanted in 178 centers in 15 countries.

Definitions

Relapse was defined as disease recurrence. Causes of death were classified as related to relapse if the patient experienced a relapse at any period during follow-up. Excess mortality was defined as the difference between mortality observed in the myelofibrosis landmark cohort and mortality in a matched cohort of the general population.

Statistical analysis

The endpoints of interest were overall survival (OS), disease-free survival (DFS), relapse/progression and non-relapse mortality (NRM) within the first 10 years after HSCT for patients alive and disease-free at the two-year landmark (LM) after HSCT. For all outcomes, patients were considered to be at risk since this LM. Median follow-up was determined using the reverse Kaplan-Meier method. OS was defined as the time since landmark until death from any cause, with surviving patients censored at the time of last follow-up. Patients still at risk at 10 years after HSCT were administratively censored. DFS was defined as time to death or relapse/progression (whichever occurred first). OS and DFS were estimated using the Kaplan-Meier product limit estimation method, and differences in subgroups were assessed by the Log-Rank test. The cumulative incidences of relapse/progression (CIR) and non-relapse mortality (NRM) were analyzed together in a competing risks framework[25]. Competing risks analyses were also applied to estimate the incidences of (extensive) chronic GVHD (cGVHD) and secondary malignancies, each with the competing event death, at 10 years after HSCT. Previous

acute GVHD (aGVHD) in the landmark population was quantified as a simple proportion, since all cases of aGVHD occurred prior to the 2-year landmark time point. Cox proportional hazards regression was used to assess the impact of potential risk factors on OS, RFS, CIR and NRM. CIR and NRM were analysed in a competing risks framework in which the cause specific hazards (CSH) were modelled.

Methods from relative survival were used to estimate the proportion of the deaths observed in our cohort which could be attributed to population causes (population mortality) and which to MF-related causes, including HSCT and pre-treatment (excess mortality)[26,27] Patients were matched by age, sex and country and year of HSCT to a cohort from the general population, for whom survival information was available in the population tables in the Human Mortality Database (http://www.mortality.org/). ~~In univariable and multivariable analyses,~~ The excess hazard of death was defined as the difference between the observed hazard in the patient cohort (this myelofibrosis cohort) and the hazard of the matched general population cohort. For multivariable analyses, we estimated Cox proportional hazards models for the excess hazard of death. Risk factors considered were age, sex, MF classification (primary versus secondary), conditioning intensity, Total Body Irradiation (TBI), donor type, stem cell source and previous GVHD (defined as the development of any type of GvHD between transplantation and the 2-year landmark). All estimates are reported with 95% confidence intervals. All analyses were performed in SPSS version 23 and R 3.3.0 (https://cran.r-project.org/), packages 'survival', 'cmprsk', 'prodlim' and 'relsurv'.

RESULTS

Characteristics of patients and transplant

Characteristics of the entire patient cohort and the long-term survivors are shown in **Table 1**. Long-term survivors were transplanted at a median age of 53.5 years, 837 (79%) patients had primary MF at the time of transplantation, 645 (63%) patients received a reduced intensity regimen and 471 (45%) were transplanted using an HLA-matched sibling donor.

Outcome and predictors for outcome

In the entire cohort including 2459 patients (without landmark), OS and DFS at 10 years were 41% (95%CI: 39-44) and 32% (95%CI: 30-35). Median follow-up in the landmark population was 49.7 months (95%CI: 47-52). In the 1055 long-term survivors, 166 deaths were registered within 10 years after HSCT. For all time periods, the most common cause of death was relapse of MF, followed by GVHD and infection, with a higher occurrence of infection-related deaths between 2- and 5-years post-transplant (**Table 2**). In the LM population, secondary cancers occurred in 34 patients before the landmark and in 87 patients after the landmark. This translated into a cumulative incidence in the LM population without cancer before the LM at 10 years of 14% (11-18) 10 years after the transplantation. The most frequent cancer was solid tumor (70% of whom 3 breast cancers), followed by acute leukemia or myelodysplastic syndrome (17%) and lymphoma (9%).

Grade 2-4 acute GVHD had occurred in 23% of the LM patients (n=245). Before landmark, 56% (576 patients) of the patients in the LM population had chronic GVHD of whom 263 patients had an extensive chronic GVHD. Among patients without chronic GVHD before the 2-year landmark, cumulative incidence of chronic extensive and limited GVHD were 13% (8-18) and 9% (5-12%), respectively. 10-year –OS and -DFS for 2-year survivors were 74% (71-78%) and 64% (60-68%) respectively (**Figure 1.** In these patients, relapse incidence and non-relapse mortality 10-years after transplant were estimated at 21% (17-24%) and 15% (12-18%) (**Figure 1**). Risk factors for mortality, DFS and relapse are shown in **Table 3**. Older age (p<0.001), type of myelofibrosis (higher risk for secondary myelofibrosis, p=0.01), male sex (p=0.004) and no GVHD before landmark (p=0.02) were associated with a significantly higher risk of mortality. Older age (p=0.033), RIC (p=0.017), male sex (p=0.003), donor other than an HLA-matched related donor (p=0.01) and no GVHD before landmark were associated significantly with lower DFS. Use of a donor other than HLA-matched related donor (p=0.008), RIC (p=0.042) and no GVHD occurrence before the landmark (p<0.001) significantly increased the risk for relapse.

Comparison to general population

The excess mortality of the two-year landmark MF cohort was 21% (18-25%) at 10-years whereas its population mortality was 4% (4-4.2%) (**Figure 2**). Excess mortality was lower in younger patients and in female gender recipients but remained considerably greater than the matched population mortality (**Figure 2**). Excess mortality in the younger cohort (< 45 years) was 14% (8-21%) and population mortality was 1% (1-1.1%) at this age. In contrast, excess mortality in the older cohort (≥65 years) was 33% (13-53%) and population mortality was 12% (10-14%).

Risk factors for late excess mortality

A Cox model was developed to estimate the risk factors for excess mortality in the 2-year disease-free survivors. Of note, the interpretation of the influence of variables in this landmark model applies to patients alive and free of the disease 2-years following transplantation. For instance, patients with severe GVHD may not survive the second year post-transplant but the subset of patients who survived with such GVHD are incorporated in the model. The multivariable model shows that older age, MF secondary to PV or ET, male gender recipient were risk factors for excess mortality (**Table 4**). In long-term survival, previous GVHD was protective for mortality (**Table 4**). The model highlights that age and sex, which were at higher risk in the general model, are still risk factors for excess mortality. **Figure 3** shows changes in the hazard of excess mortality of for reference patients according to Cox model (variables from the **Table 4**) transplanted at the age of 50 years, the hazards are given for men and for women separately. We can see that there is a decline in hazard of excess mortality over time post HSCT but after 3 years (5 years post-transplant), there is a ~~kind of~~ plateau.

DISCUSSION

This EBMT report of 1055 patients alive and in remission at 2-years after HSCT is the largest study of long-term post-transplant outcome in patients with MF. Results indicate that survival 10 years after transplantation in these 2-year survivors is 74% but also that the mortality rate does not decrease to that expected in the general population. This is the first long-term study in myelofibrosis with the method of landmark analysis. Previously, it has been reported in other diseases that long-term outcome in transplanted patients remains lower than expected in general population (except in aplastic anemia)[20] [21]. Our results can be considered disappointing as compared to previous publications, especially from CIBMTR, but the median age was 2 decades higher in our cohort which could explain the higher long-term mortality. Indeed, we could confirm that in a subgroup of patients younger than 45 years, OS was very good OS at 86% 10-years after transplantation. Two additional recent long-term analyses in patients with chronic malignancies (chronic lymphocytic leukemia (CLL) and myelodysplastic syndrome (MDS)) from EBMT registry included patients with a median age closer to MF patients, estimated long-term survival lower than in this MF cohort[2724]. Similar risk factors for mortality were found with a better OS in women and in younger[24] patients. The higher risk in male recipients is not totally elucidated but usually it is thought to be possibly due to higher risk behavior and also to higher propensity towards comorbidities such as cardio-vascular disease[28]. In contrast, an EBMT study led in patients with acute myeloid leukemia did not show age and sex were predictors for OS[29].

Akin to other malignant disorders, late relapse was the leading cause of death in MF patients following HSCT [19–22,24,29]. Relapse incidence at 10-years after transplant in the long-term survivors is 21%, concordant with that expected in other malignant disorders and highlights that even if the relapse risk decreases over time, it can still occur late after transplant. Many studies have reported that relapse risk is related to the disease risk at the time of transplant. Unfortunately, due to the retrospective registry-based nature of this study, we did not have sufficient data to calculate a relevant IPSS and so unfortunately could not analyze this aspect. However, we observed that the relapse risk was higher in patients who received a RIC, which could be expected but were surprised that in long-term survivors, the intensity of the regimen still had some impact. In acute myeloid leukemia, the EBMT long-term study, did not find that regimen intensity still has influence on late relapse[29]. Occurrence of acute or chronic GVHD before the landmark was the strongest factor preventing relapse in long-term survivors[17,1817,1817,1817,18]. While in many other studies, GVHD increased the risk of late deaths, we failed to confirm this assertion in our MF cohort[19,20]. GVHD before landmark (2 years) in long-term survivors was protective for both relapse risk as well as for mortality. Of course, from this analysis, we cannot extrapolate that GVHD is needed to improve long-

term outcome, because patients with GVHD leading to death in the first 2 years of transplant have been excluded from the study~~, per se~~.

The weakness for GVHD analysis within this cohort was that we could not delineate the risk of "active GVHD" because we had no data regarding GVHD resolution, albeit that it is probable that patients still alive at 2 years with chronic GVHD were those with the less severe GVHD. The vast majority of patients had onset of chronic GVHD before the landmark but some patients had also a late onset. Finally, the majority of survivors suffered (or had suffered) from chronic GVHD which may alter their quality of life and it is noteworthy that even if they are in remission from their myelofibrosis, patients could have a chronic GVHD which can be a cause of death especially before 5 years.

Infectious complications remained a frequent cause of death between 2 and 5 years post-transplant. It has been previously reported that splenectomy before transplant increased the risk of late severe infection which may in part contribute to these findings within the MF-cohort[30]. This high risk of lethal infection should be taken into account in long-term monitoring strategies and highlights the importance of appropriate anti-infective prophylaxis[31,32].

Second malignancies were also the cause of very late deaths, justifying long-term monitoring and cancer prevention in this population. After 5-years, 16% of deaths were due to second malignancies and at 10 years, cumulative incidence of secondary cancer was 14%. We could not analyze specific risk factors for second malignancies due to the small numbers involved. There are few long-term survivors for non-transplanted higher risk MF so there is no data for long-term secondary cancers within that population is unknown. It is hard to determine how the transplantation process increases the risk of cancer but chemotherapy, radiotherapy, immune deficiency, chronic GVHD, genetic susceptibility as well as age can cumulatively contribute towards an increased susceptibility.

To conclude, patients with MF have good survival when alive and in remission 2-years after transplantation, especially younger and female recipients. Severe late complications and late relapses should be monitored and prevention highlighted in order to reduce life threatening complications. Lifelong follow-up is required to optimize long-term outcomes[33].

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Author contributions: MR, YC and NK designed the study, LDW and DJE did statistics, NSK did data management, MR, YC, NK, DML analyzed the data, MR, CW, JS, MTVL, DB, AB, DN, AV, WB, RA, JF, LV, IYA, AN, XP, HE, PC, EH, PL, ST, AR and NK provided the patients, MR wrote the paper, all co-authors had opportunity to discuss results and approved the final manuscript.

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Table 1. Patients and transplant characteristics

	Whole cohort		2-year land mark	
	Numbers	%	Numbers	%
Total number of patients	2459		1055	
Disease at time of transplant				
Primary myelofibrosis	1904	78	837	79
Secondary myelofibrosis	421	17	188	18
Transformation into acute leukemia	134	5	30	3
Median age at HSCT, years	55		53.5	
Age < 45 years	355	14	193	19
Age 45-54 years	729	30	351	33
Age 55-64 years	1137	46	426	40
Age >= 65 years	238	10	85	8
Interval primary diagnosis and transplant				
Median			26.7	
< 12 months	743	30	308	29
>=12 months	1716	70	747	71
Conditioning regimen				
Reduced intensity	1502	63	645	63
Standard	877	37	378	37
Total body irradiation Yes	423	17	191	18
No	2015	83	855	82
Source of stem cells				
Marrow	332	14	150	14
Blood	2127	86	905	86
HLA matched sibling donor	1022	43	471	45
Other	1379	57	565	55

Unreported data found for regimen and type of donor but always < 4%.

Table 2. Causes of mortality after 2 years

Years from transplant	2 - 5y		>5 - 10y	
	N	%	N	%
Relapse/progression	33	41	30	61
Secondary malignancy*	9	11	8	16
GvHD	18	22	9	19
Infection	17	21	2	4
Organ damage/toxicity	4	5		
Unknown	28		8	
Total	109		57	

* including post-transplant lymphoproliferative disease

Table 3. Multivariable (cause-specific) Cox proportional hazards models for outcomes in the period between 2 and 10 years after HSCT for patients alive and disease-free at 2 years after HSCT

Variables	Overall survival	P-value	Disease-free survival	P-value	Relapse	P-value
	HR (95%CI)		**HR (95%CI)**		**HR (95%CI)**	
Age (per decade)	**1.45 (1.19- 1.76)**	**<0.001**	**1.18 (1.01 - 1.37)**	**0.033**	1.16 (0.96 - 1.42)	0.131
Patient sex						
Male	1		1		1	
Female	**0.58 (0.4 - 0.84)**	**0.004**	**0.65 (0.49 - 0.87)**	**0.003**	0.79 (0.55 - 1.14)	0.205
MF classification						
PMF	1		1		1	
SMF	**1.66 (1.13 - 2.44)**	**0.01**	1.35 (0.97 - 1.88)	0.071	1.07 (0.67 - 1.7)	0.78
Source of stem cells						
Marrow	1		1		1	
PB	0.83 (0.51 - 1.34)	0.442	0.77 (0.52 - 1.13)	0.178	0.67 (0.41 - 1.09)	0.107
Cond. reg. intensity						
MAC	1		1		1	
RIC	1.17 (0.79 - 1.73)	0.434	**1.48 (1.07 - 2.04)**	0.017	**1.54 (1.02 - 2.35)**	0.042
Cond. reg. with						
Chemo only	1		1		1	
TBI	1.25 (0.81 - 1.93)	0.322	1.28 (0.89 - 1.82)	0.18	1.28 (0.8 - 2.06)	0.305
Type of donor						
Matched sibling	**1**		1		**1**	
Unrelated	1.08 (0.77 - 1.51)	0.669	**1.43 (1.09 - 1.89)**	**0.011**	**1.65 (1.14 - 2.39)**	**0.008**
Any previous GVHD	**0.67 (0.48 - 0.94)**	**0.02**	**0.62 (0.47 - 0.81)**	**0.001**	**0.42 (0.3 - 0.6)**	**<0.001**

Table 4. A multivariable Cox proportional hazards model for excess mortality in the period between 2 and 10 years after HSCT for patients alive and disease-free at 2 years after HSCT

	Hazard ratio	95% confidence interval	P-value
Patient sex			
Male	1		
Female	0.62	0.41 - 0.93	0.022
Age (per decades)	1.35	1.08 - 1.69	0.008
Disease			
Primary myelofibrosis	1		
Secondary myelofibrosis	1.81	1.18 - 2.78	0.007
Standard	1		
Reduced intensity regimen	1.16	0.74 - 1.82	0.527
No TBI	1		
TBI in regimen	1.25	0.75 - 2.08	0.384
Donor			
Matched sibling donor	1		
Other donor	1.1	0.75 - 1.63	0.623
Source of stem cells			
Marrow	1		
Blood	0.83	0.48 - 1.44	0.515
GVHD			
No	1		
Any	0.65	0.44 - 0.96	0.031

Legends to Figures

Figure 1. Outcome of myelofibrosis patient from landmark time

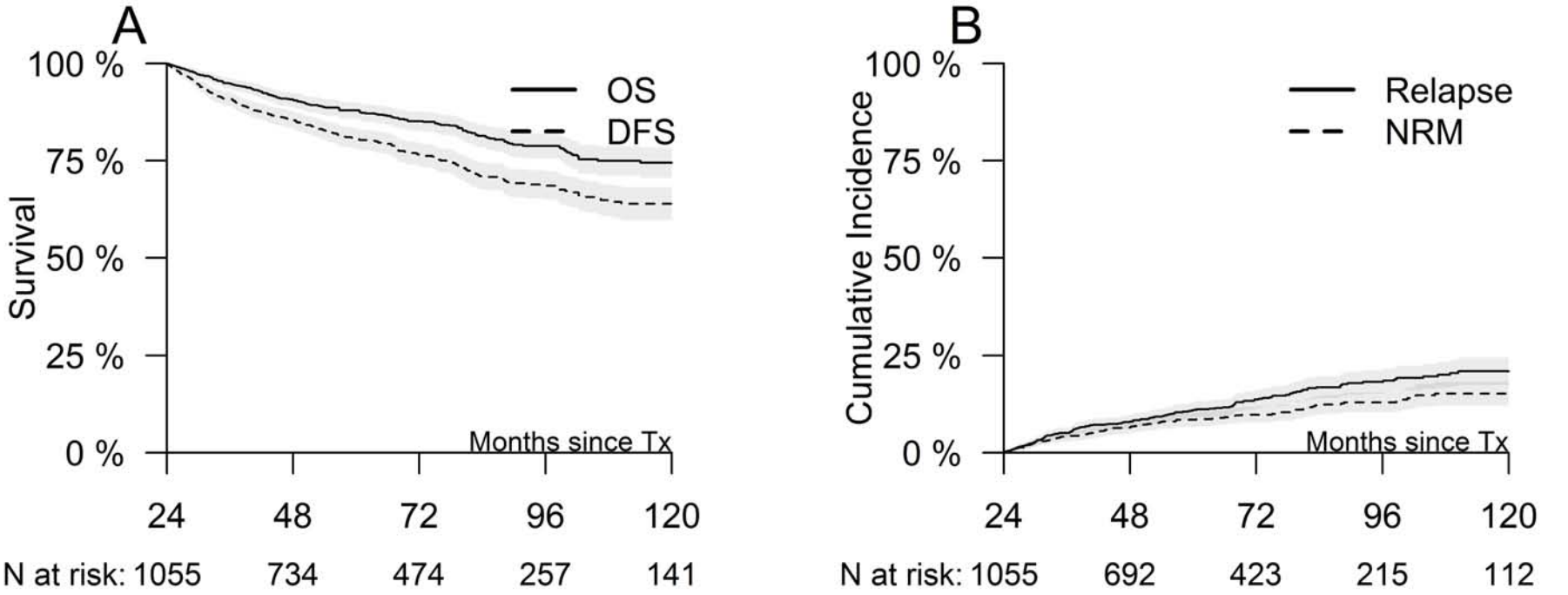
Left panel: overall Survival and Disease Free Survival from landmark time. Solid line is OS, dashed line is DFS. Right panel: relapse incidence and non-relapse mortality. Solid line is relapse, dashed line is non-relapse mortality.

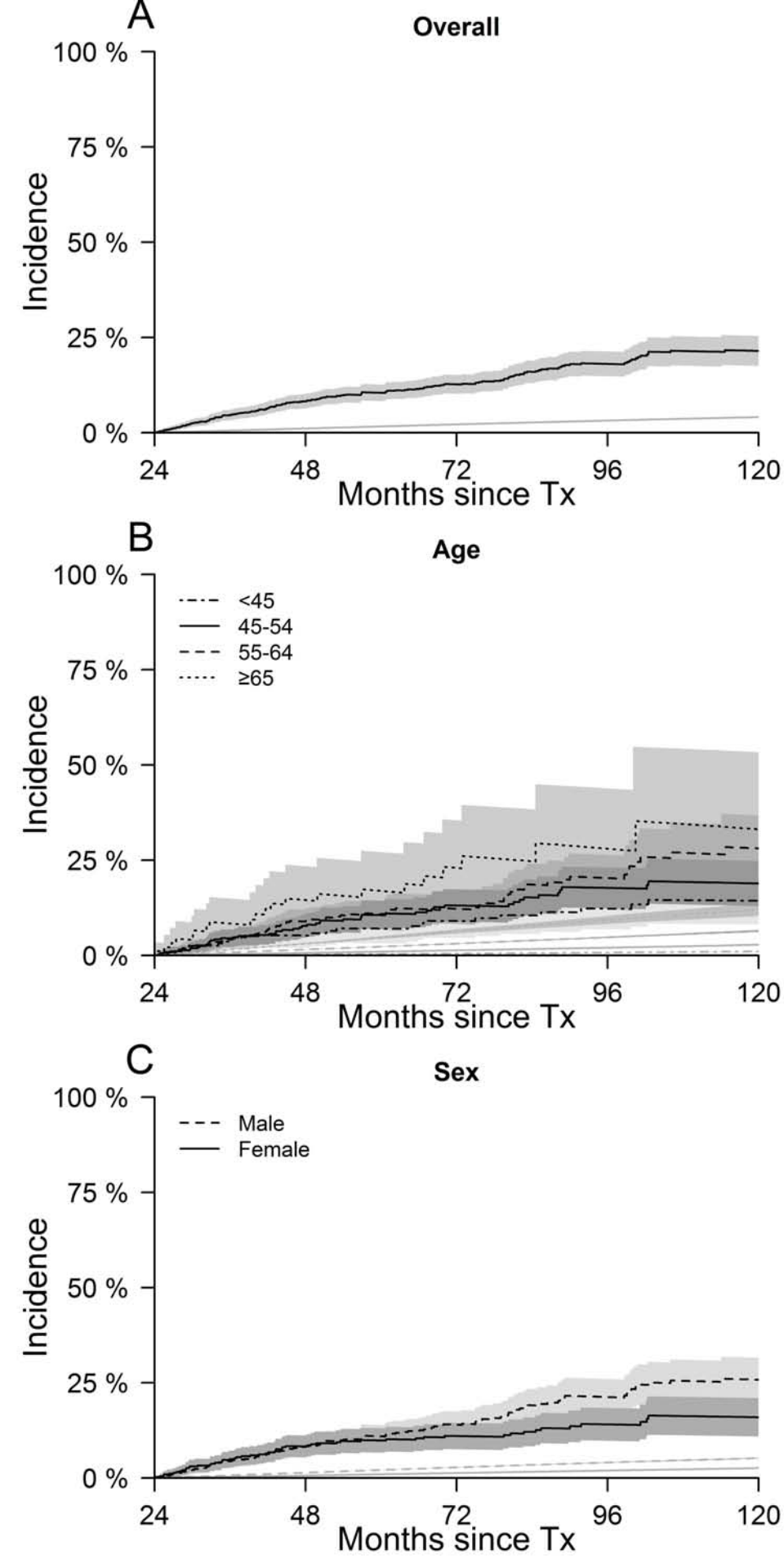
Figure 2. Mortality in myelofibrosis compared to general population

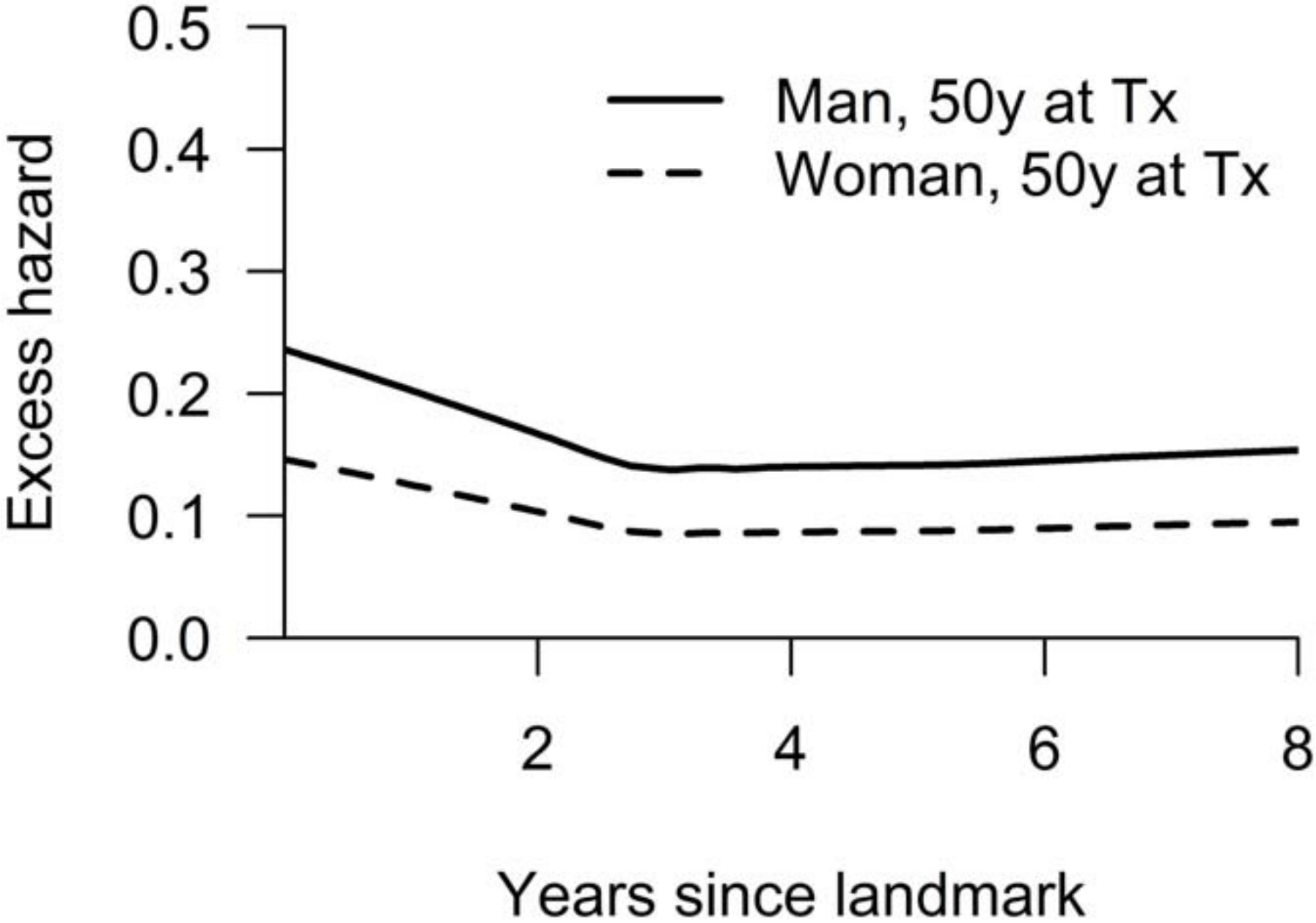
Top figure: The plots show mortality of the disease-free survivors (black line) and in general population (grey line) mortality. Middle figure: The plots show mortality of the myelofibrosis patients according to sex (black solid line in female and dashed line in male) and the mortality in the general population (grey lines). Down figure: the plots show mortality of disease-free survivors (black lines) and general population (grey lines) by age categories

Figure 3. Hazard rate for excess risk of mortality with post-transplant time

The curves show hazard rates for two reference patients, based on the Cox model for the excess hazard. They are both 50 years at HSCT, had primary MF, received standard conditioning, no TBI, a matched sibling donor, marrow as source of stem cells and no previous GVHD. The solid line shows a male patient and the dashed line a female patient.


A
100 %
75 %
50 %
25 %
0 %
Survival
OS
DFS
Months since Tx
24
48
72
96
120
N at risk: 1055
734
474
257
141
B
100 %
75 %
50 %
25 %
0 %
Cumulative Incidence
Relapse
NRM
Months since Tx
24
48
72
96
120
N at risk: 1055
692
423
215
112


A
Overall
100 %
75 %
50 %
25 %
0 %
Incidence
24
48
72
96
120
Months since Tx
B
Age
<45
45-54
55-64
≥65
100 %
75 %
50 %
25 %
0 %
Incidence
24
48
72
96
120
Months since Tx
C
Sex
Male
Female
100 %
75 %
50 %
25 %
0 %
Incidence
24
48
72
96
120
Months since Tx


0.5
0.4
0.3
0.2
0.1
0.0
Excess hazard
Man, 50y at Tx
Woman, 50y at Tx
2
4
6
8
Years since landmark