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Platelet recovery delay and survival in patients with myelofibrosis undergoing allogeneic hemopoietic stem cell transplantation

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ABSTRACT

We studied platelet recovery in 93 patients with myelofibrosis, following an allogeneic hemopoietic stem cell transplant (HSCT). The primary end point of the study was achieving a platelet count of 50x10^9/L within day +100, which occurred in 62 patients (67%) and predicted 5 year non relapse mortality (5% vs 55%; p=0.0009) and 5 year actuarial survival (85% vs 38%; p=<0.00001). Relapse was unaffected. The cumulative incidence of strong platelet recovery was predicted by a matched sibling donor (MSD), compared to alternative donors (90% vs 60%, p=.001), by the dose of CD34+ cells (cut off 8.68x10^6/kg) (83% vs 61%, p=0.01), recipient age (cut off 63 years) (72% vs 48%, p=0.01), and splenectomy (86% vs 63%, p=0.04). In multivariate Cox analysis, significant predictors were a MSD (p=0.003), a high CD34 cell dose (p=0.02) , splenectomy (p=0.003) and younger patients (p=0.02). Patients with slow platelet recovery, have significantly lower platelet counts long term, combined with chronic graft versus host disease. In conclusion strong post-HSCT platelet recovery in MF patients, is mainly predicted by donor type, together with CD34 cell dose, patients age, and is strongly associated with NRM and survival.

INTRODUCTION

Delayed platelet recovery has been described to occur in a significant proportion of patients, following an allogeneic hemopoietic stem cell transplant (HSCT) **(1) ,** and has been associated with increased non relapse mortality NRM **(1-4).** Predictors of delayed recovery include low CD34 cell dose **(5),** graft versus host disease (GvHD) **(4)**, age, performance score and donor type **(1-2).** Hematologic recovery is of particular importance in patients with myelofibrosis (MF) undergoing an allogeneic HSCT, since two hallmarks of the disease are bone marrow fibrosis (graded from MF1 to MF3), and splenomegaly **(6).** Both these two factors can delay recovery either by trapping progenitors in the enlarged spleen, and/or by providing a fibrotic marrow environment, unsuitable for stem cell homing. In a study comparing MF and leukemia patients after an allogeneic HSCT, the number of circulating CD34 cells post-transplant, was significantly reduced in MF patients, suggesting spleen pooling **(7);** bone marrow sections exhibited reduced VCAM-1 expression, a key adhesion molecule on endothelial cells, suggesting a microenvironment less suitable for stem cell homing **(7).** Prolonged cytopenia results in prolonged transfusion dependence, poor graft function (PGF) and elevated non relapse mortality (NRM): the 5 year survival of patients with PGF is reported to be 14% **(8).**

The aim of this study in MF patients undergoing an allogeneic HSCT, was to identify a surrogate marker of strong hematologic recovery, better predicting NRM and survival, and subsequently assess pre-HSCT and HSCT factors, predicting hematologic recovery.

METHODS

Patients who underwent a first HSCT for myelofibrosis at our transplant Centre between year January 2016 and June 2024 , alive on day +20 post-transplant, who achieved a neutrophil count of 0.5x10^9/L, were included in the study. Assessed were time to a neutrophil count of 0.5x10^9/L, time to a platelet count of 20x10^9/L and time to a platelet count of 50x10^9/L. Variables studied were disease related (DIPSS, degree of marrow fibrosis-MF1,2,3-, driver mutations, spleen size), treatment related (splenectomy, ruxolitinib, transfusion burden), transplant related (conditioning regimen, GvHD prophylaxis, donor type , gender and age) patient age and gender. Spleen size was recorded as the largest spleen size in the clinical history of the patient.

Transplant procedures. The selection of donors was prioritized as follows: HLA identical sibling donors (MSD) , HLA matched (8/8) unrelated donors (MUD) , 7/8 HLA matched unrelated donors (UD) and haploidentical family donors (HAPLO). The conditioning regimen was a combination of thiotepa (10 mg/kg), fludarabine 150 mg/m^2 and intravenous busulfan (3.2 mg/kg/day in 4 separate doses) for two consecutive (n=65) or 1 day (n=23) (TBF); 5 patients received a non myeloablative regimen including fludarabine, cyclophosphamide and total body irradiation 2 Gy. The stem cell source was peripheral blood (n=73) or bone marrow (n=20).

We have used only two regimens of GvHD prophylaxis : regimen A consisted of cyclosporine (CSA)(3 mg/kg i.v) (day-1 onwards) methotrexate 10 mg/m^2 (MTX) (day +1+3+6+11) anti-thymocyte globulin (ATG) (Rabbit Thymoglulin , Sanofi, France, 4.5 mg/kg) (n=13); regimen B = post transplant cyclophosphamide (PTCY) 50 mg/kg day +3+4, combined with CSA day +5 onwards and mycophenolate (MMF),day +5 untill day +30.

The study was conducted in accordance with the Helsinki criteria and obtained approval from the Gemelli Ethical Committee (ID 4751 Prot 6539/22). All patients provided written informed consent for research studies using an Institutional form, approved by the Ethical Committee.

Chimerism studies and definition of full donor chimerism: chimerism was assessed by PCR analysis of short tandem repeats (STR). The proportion of donor recipient chimerism was calculated using the PowerPlex Fusion System (Promega, srl, Italy) on 24 STR loci. Full donor chimerism (F-DC) was defined as having >95% donor alleles.

Statistical analysis

Descriptive statistics included medians for continuous variables, and contingency tables for dichotomous variables. The cumulative incidence (CI) of platelet recovery was calculated using death without a platelet recovery as a competing event. The CI of acute or chronic GvHD were calculated with death, in the absence of acute or chronic GvHD, as competing event. Survival curves were generated using Kaplan-Meier analysis. The cumulative incidence of NRM was calculated with relapse as a competing event, and viceversa. All statistical analyses were run on the NCSS 2019 Statistical Software (NCSS, LLC, Kaysville, Utah, USA -ncss.com/software/ncss).

RESULTS

Hematologic recovery and outcome. All patients achieved a neutrophil count of 0.5x10^9/L at a median interval of 22 days (11-70). The median time to a platelet count of 20x10^9/L, for 85 patients, was day 32 (range 11-159); We then identified the strongest marker of hematologic recovery, which would affect NRM. The difference in time to a neutrophil count of 0.5x10^9/L was not predictive (p=0.3); the difference in time to a platelet count of 20x10^9/L was significantly shorter in patients without NRM (p=0.01); the difference in time to a platelet count of 50x10^9/L was highly significantly different in patients with NRM (p=0.0001). This was confirmed with a ROC analysis of platelet counts within day +100, against NRM, which identified a platelet count of 50x10^9/L, as the best cut off , with a sensitivity of 85% and a specificity of 78% Therefore, patients were stratified in 2 groups, according to whether they achieved a platelet count of 50x10^9/L within day +100 or not. **Table 1** outlines clinical characteristics of these two groups. A platelet count greater than 50x10^9/L , within day +100, was achieved overall in 62 patients (67%), at a median interval of 40 days (range 15-98), which was confirmed by cumulative incidence analysis (67%, 95%confidence interval 58%-77%).

Outcome.

The overall cumulative incidence of non relapse mortality (NRM) was 20% at 5 years (95%CI 13-30%). A platelet count of 50 x10^9/L within day +100, predicted 5 year NRM (5% vs 55%; p=0.00009) **(Fig.1a)** and 5 year actuarial survival **(Fig.1b)** (85% vs 38%; p=<0.00001). Relapse at 5 years was unaffected by hematologic recovery (19% and 22% ;p=0.5). The cumulative incidence of acute GvHD grade II-IV was 19% (11-32%) vs 42% (27-63%) in patients with or without a platelet count of 50 x10^9/L within day +100 (Gray test p=0.02). The 3 year cumulative incidence of moderate/severe chronic GvHD was 20% (14-35%) vs 46% (30-67%) (Gray test 0.02) ; the CI of severe chronic GvHD was 2% (95%CI 0.2-11%) vs 19% (95%CI 11-39%) in patients with or without a platelet count of 50 x10^9/L within day +100 (Gray test p=0.003).

Predictors of early platelet recovery. Table 2 outlines factors predictive of early strong platelet recovery, in univariate analysis; donor type (MSD) , younger patients age, higher CD34 cells infused, and splenectomy. In a multivariate Cox analysis , transplants from a matched sibling donor, remained the most significant predictor (p=0.003), followed by

splenectomy (p=0.004), a high CD34 cell dose (p=0.02) and older age (p=0.02)**(Table 2)**. Donor and patients gender and age, primary or secondary disease, DIPSS risk category, MTSS risk category, driver mutations, transplant year > 2019, conditioning regimen intensity, GvHD prophylaxis, maximum spleen size, transfusion burden pre-transplant, graft source did not influence strong platelet engraftment **(Table 2)**. We have also run a linear regression analysis, between maximum platelet counts and conditioning intensity, and found no correlation. When looking in detail at donor type, we found strong platelet recovery in 90% MSD (n=20), 55% in HAPLO (n=20), 62% in MUD (n=40) and 62% in mismatched UD (n=13). Driver mutations did not seem to affect platelet recovery (JAK2, 45/69, CALR, 8/14, MPL, 4/5 and triple negative 5/5, p=0.3). ABO mismatch also had no significant impact on strong platelet recovery: ABO match 65%), ABO major mismatch (60%), ABO minor mismatch (75%), only 2 patients double ABO mismatch (p=0.5). Because splenectomy is less likely to be currently performed, we wanted to combine donor type, CD34 cell dose and age, using ROC cut off values for age (62 years) and CD34 dose (8,41x10^6/kg). We identified 3 separate groups of patients with 0-1 (n=33), 2 (n=42) and 3 adverse predictors (n=18). The cumulative incidence of achieving a platelet count of 50x10^9/L was respectively 91%, 57% and 44% (p=0.00007) **(Fig.2a)**; 5 year actuarial survival, in these 3 groups of patients, was 89%, 65%, 43%, p=0.003) **(Fig.2b).** Non relapse mortality in the three groups was 3% (95%CI 0.4-20%), 25% (14-42%) and 42% (23-73%) (Gray test 0.003)

Long term follow up. Platelet counts after HSCT are shown in **Fig.3:** patients who failed to achieve a platelet count of 50x10^9/L within day +100 (Group B) show significantly lower platelet counts up to 4 year after HSCT, as compared to patients with robust early platelet recovery (Group A).

Chimerims and platelet recovery. A strong platelet recovery was achieved in 66% of patients with full donor chimerism (n=75) and 66% in patients with mixed donor chimerism (n=18).

Causes of death. The primary cause of death for patients achieving a platelet count of 50x10^9/L vs patients not achieving this count are as follows: relapse 6-3; GvHD 1-6; graft failure 0-1; cardiac toxicity 0-1; infection 2-4; multiorgan toxicity 1-5 (p=0.004).

DISCUSSION

We have shown in this study that patients with myelofibrosis, achieving a platelet count of 50x10^9/L within day +100, following an allogeneic transplant, have a significantly lower risk of non relapse mortality (NRM) (p=0.00009) and significantly improved survival (p<0.00001), whereas relapse was unaffected. A more conventional end point of 20x10^9/L platelets within day+30 or within day +50 was less predictive of NRM. The same platelet count (50x10^9/L) was identified in a study by the Minnesota group, looking at predictors of delayed recovery and NRM **(1):** in a group of 850 patients with malignant and non malignant disease, failure to achieve a platelet count of 50x10^9/L, within day 60 after HSCT, was identified as delayed platelet recovery (DPR)**(1):** platelet recovery was seen in 40% cord blood grafts, 57% in unrelated donor (URD) and 74% in MSD transplants. In this study we have selected only patients with myelofibrosis, and have chosen 50x10^9/L platelets as a strong marker of robust hematologic recovery: the primary end point of this study was to identify predictors of platelet recovery. In univariate and multivariate analysis a transplant from an HLA identical sibling was the most significant positive predictor, followed by a higher number of CD34 cells infused, splenectomy , and younger age . There was a trend for better recovery in patients with fibrosis less than MF3. There was no effect of driver mutations, DIPSS, MTSS, conditioning regimen, pre-transplant ruxolitinib, or GvHD prophylaxis with PTCY. As to donor type, our finding confirms that MSD is the best donor for MF patients. In a prospective study, there was a very strong impact of donor type on survival **(9):** non relapse mortality was 22% for matched siblings and 59% for alternative donors, and engraftment was 97% vs 76%. The actuarial five year survival was 35% for alternative donors **(9).** Similar outcome was shown in an other study, with 31% five year survival for alternative donor grafts **(10).** On the other hand, in patients with acute leukemia the outcome of transplants from MSD and alternative donors, appears to be quite comparable **(11,12).** This difference between acute leukemia and MF, may be due to the inflammatory nature of MF, which is aggravated after an allogeneic transplant, and calls indeed for improved GvHD control. A recent study with peri-transplant ruxolitinib appears to have reduced GvHD and improved outcome **(13);** similarly, the use of a CD34 selected stem cell graft , appears to go in the same direction, reduced inflammation, and excellent results have been reported, with an 88% three year survival **(14).**

The second strong predictor of early platelet engraftment is a high number of CD34 cells infused : this has already been identified as a positive indicator of outcome in an

EBMT study **(15),** with a significant impact on survival, relapse free survival , and non relapse mortality. A word of caution should be spent when using high dose CD34 cells, which may result in a high incidence of GvHD, and may call for augmented GvHD prophylaxis **(16).** The third predictor of a fast and strong platelet engraftment in our study was splenectomy, again in keeping with registry based studies **(17):** patients grafted after splenectomy had significant reduced NRM, though increased relapse, resulting in comparable survival with non splenectomized patients **(18).** Other measures to reduce spleen size, and therefore spleen pooling, would be new JAK inhibitors **(19)** and splenic irradiation **(20).** Finally older age in our series, was associated with a significant lower cumulative incidence of strong platelet recovery, both in univariate and multivariate analysis. Again older age is a well known predictor of outcome in patients undergoing an allogeneic HSCT, so this finding in MF, comes as no surprise. We then wanted to further predict the incidence of strong platelet recovery, and decided to exclude splenectomy, since it is currently rarely performed, and in our Unit, it has not been used in the past 4 years. We restricted this model to donor type, CD34 cell dose (cut off 8,41x10^6/kg) and patients age (cut off 62 years). Patients with 0-1 , 2 or 3 negative predictors had a cumulative incidence of strong platelet recovery, respectively, of 90%, 58%, 43% (p=0.00008), and an actuarial 5 years survival of 90%, 60%, 42% (p=0.003). Therefore it is possible to identify, at the time of transplant, patients who will be at high risk of poor graft function and non relapse mortality. We have also tested the MTSS score **(21)** , which predicted survival but not significantly platelet recovery.

Finally, patients who fail to achieve a platelet count of 50x10^9/L within day 100, continue to have significantly lower counts, up to 4 years post transplant and beyond: we were unable to find in the literature, reports on long term hematologic recovery in MF patients, following an allogeneic HSCT. We show in this study that moderate severe chronic GvHD was seen in 46% of patient with long lasting low platelet counts, despite the majority of them (over 90%) had received post transplant cyclophosphamide for GvHD prophylaxis. Indeed GvHD is associated with reduced stem cell pool and poor peripheral blood cell counts : in a detailed study on 126 allografts, patients with GvHD had significantly lower peripheral blood counts, granulocyte macrophage colony forming units (CFU-GM) and erythroid burst forming units (BFU-E), as compared to patients without GvHD, (**22),** all possibly due to inflammatory cytokines**.** These results would support transplant platforms aimed at

reducing GvHD, such as the use of CD34 selected cells **(14)** or peri-transplant rituximab **(13).**

Limits of this study are its retrospective nature, and the relatively small number of patients. Nevertheless, the identification of predictors for strong platelet recovery in myelofibrosis, and therefore of NRM, may be useful when selecting patients and CD34 cell dose: a patient over the age of 62 with an alternative donor, will have a risk of poor graft function of 43% at day 100, and a NRM of 25%; a high dose of CD34 cells may well be required in this patient. On the other hand, a young patient (<62 year old) with a MSD, will have a very low NRM and a high probability of fast platelet recovery: the CD34 cell dose may not be crucially important. We have also shown low platelet counts long term, combined with significant GvHD, suggesting that PTCY may not be sufficient GvHD prophylaxis for MF undergoing an alternative donor graft. These data would support trials looking at a high CD34 cell dose **(14)** combined with peri-transplant rituximab**(13)**, in patients undergoing alternative donor grafts.

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Table 1. Clinical characteristics of patients with/without a platelet recovery of 50x10^9/L within day +100)

Variable	Plt 50x10^9/L within day+100		P
	NO	YES	
Number of patients	31 (33%)	62 (67%)	
Donor age yy median (range)	30 (19-63)	31 (20-61)	0.5
Donor gender M/F	24/7	47/15	0.3
Rec.age, yy; median (range)	59 (42-73)	56 (36-69)	0.05
Recipient gender M/F	19/12	34/28	0.5
ABO major mismatch n.pts (%)	12 (39%)	18 (29%)	0.5
Donor : HLA id SIB	2 (6%)	18 (29%)	0.01
Spleen >20 n.pts (%)	12 (38%)	24 (38%)	1.0
Transf > 20 n.pts (%)	9 (29%)	12 (19%)	0.2
DIPSS high risk; n.pts (%)	11 (35%)	24 (39%)	0.7
MTSS high risk n.pts (%)	10 (32%)	15 (24%)	0.4
Fibrosis MF3; n.pts (%)	28 (90%)	46 (74%)	0.06
Pre-Tx ruxo¸ n.pts (%)	23 (74%)	45 (72%)	0.8
Splenectomy n.pts (%)	2 (6%)	12 (19%)	0.1
PTCY ; n.pts (%)	29 (94%)	51 (82%)	0.1
Comorb.index >2; n.pts (%)	19 (61%)	26 (42%)	0.07
Myeloablative condit.; n.pts (%)	21 (68%)	43 (69%)	0.9
CD34x10^6/kg median (range)	5.68 (1.7-11.9)	6.3 (1.6-15.0)	0.05

Abbreviations: yy= years; Plt= platelets;pts=patients;Transf= transfusions; M/F= male /female; Rec.age=recipient age; HLA id SIB= HLA identical sibling; alt don= alternative donor; DIPSS= dynamic international prognostic scoring system; Pre-Tx ruxo = pre transplant ruxolitinib; PTCY= post transplant cyclophosphamide for GvHD= graft versus host disease;29

Table 2. Univariate and Multivariate Cox regression model on achieving a platelet count of 50x10^9/L ; disease and transplant variables

Variable	Value	comp	Univariate		Multivariate		
		RR	P		RR	(95%CI)	P
Splenectomy	no	yes	1.87	.05	3.11	(1.54- 6.26)	.004
Transfusions (n)	<20	≥20	0.69	.21			
Spleen (cm)	<20	≥20	0.98	.94			
DIPSS	<high	high	0.96	.90			
MTSS	low	>low	0.72	.24			
Fibrosis MF3	no	yes	0.65	.14			
Comorbidity	<=2	>2	0,68	.14			
Donor type	MSD	alt d	0.44	.002	0.42	(0.23-0.74)	.003
Recip. Age (yy)	continuous		0.47	.02	0.96	(0.93-0.99)	.03
Conditioning	MA	RIC	.96	.90			
CD34 x10^6/kg	continuous		1.85	.02	1.11	(1.01- 1.22)	.02
PTCY	no	yes	0.57	.09			

Abbreviations: DIPSS= dynamic international prognostic scoring system; MTSS= clinical-molecular myelofibrosis transplant scoring system ; PTCY= post transplant cyclophosphamide GvHD prophylaxis

Legend for Figures

Figure 1 The overall cumulative incidence of non relapse mortality (NRM) and of relapse in the 2 group (with or without a platelet count greater than 50x10^9/L within day +100)

Figure 1a. Cumulative incidence of non relapse mortality (NRM).

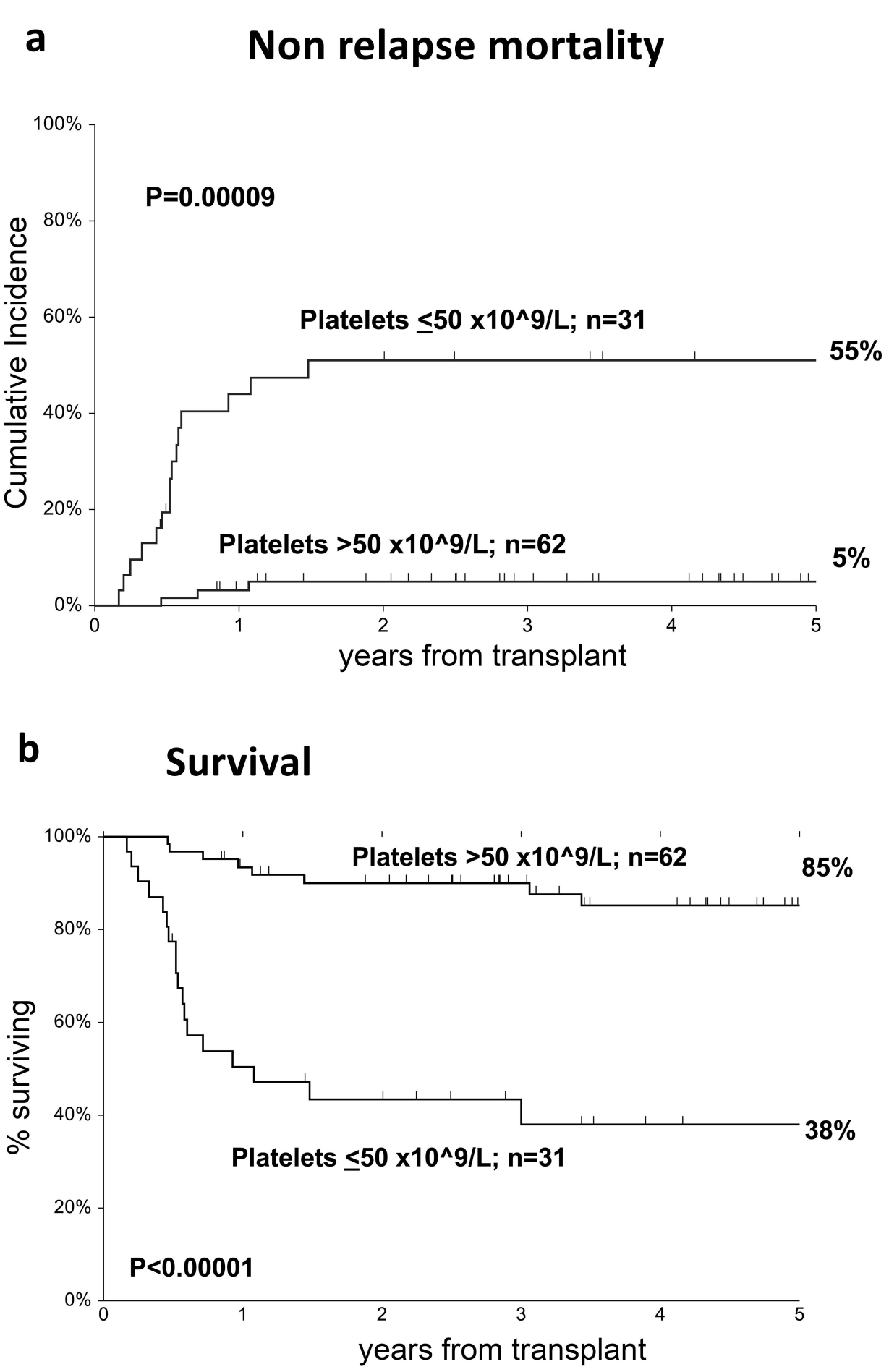
Figure.1b. Cumulative incidence of relapse, which is comparable in the two groups.

Figure 2. Platelet recovery, (50x10^9/L) within 100 days after transplant: and survival at 5 years stratified for 3 groups of patients according to 3 negative predictors: CD34 cells infused x10^6/kg <8.41; age <62 years, and donor other than MSD.

Figure 2a. Cumulative incidence of platelet recovery, (50x10^9/L) within 100 days after transplant: stratified are 3 groups of patients according to 3 negative predictors: CD34 cells infused x10^6/kg <8.41; age <62 years, and donor other than MSD.

Figure 2b. Actuarial survival at 5 years of the same 3 groups of patients.

Figure 3. Median platelet counts of the two groups with fast **(group A)** or slow **(group B)** platelet recovery within day +100. The latter group exhibits significantly lower platelet counts long term, beyond 5 tears after transplantation.


a
Non relapse mortality
100%
80%
60%
40%
20%
0%
Cumulative Incidence
P=0.00009
Platelets ≤50 x10^9/L; n=31
55%
Platelets >50 x10^9/L; n=62
5%
0
1
2
3
4
5
years from transplant
b
Survival
100%
80%
60%
40%
20%
0%
% surviving
Platelets >50 x10^9/L; n=62
85%
38%
Platelets ≤50 x10^9/L; n=31
P<0.00001
0
1
2
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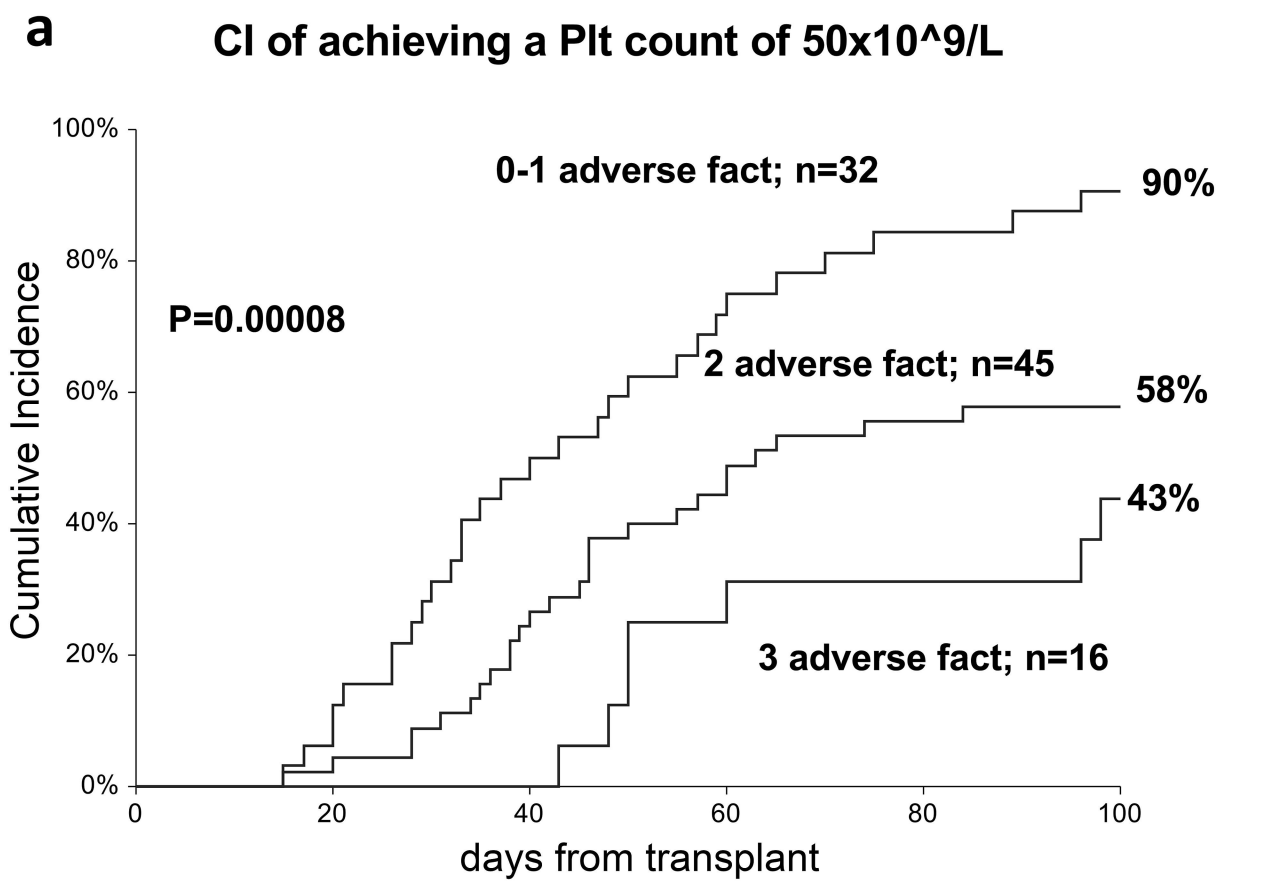
4
5
years from transplant


a
CI of achieving a Plt count of 50x10^9/L
100%
80%
60%
40%
20%
0%
Cumulative Incidence
0-1 adverse fact; n=32
90%
P=0.00008
2 adverse fact; n=45
58%
43%
3 adverse fact; n=16
0
20
40
60
80
100
days from transplant

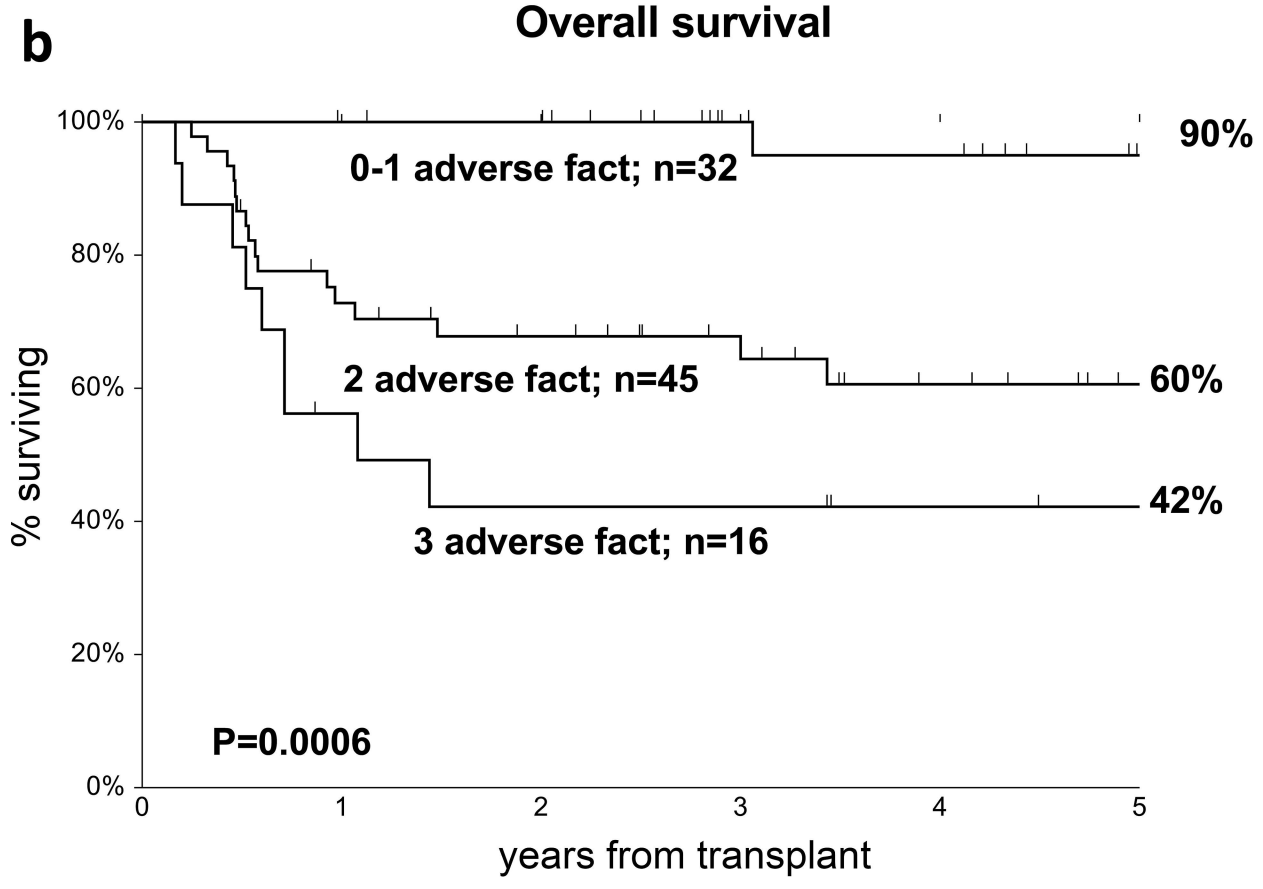
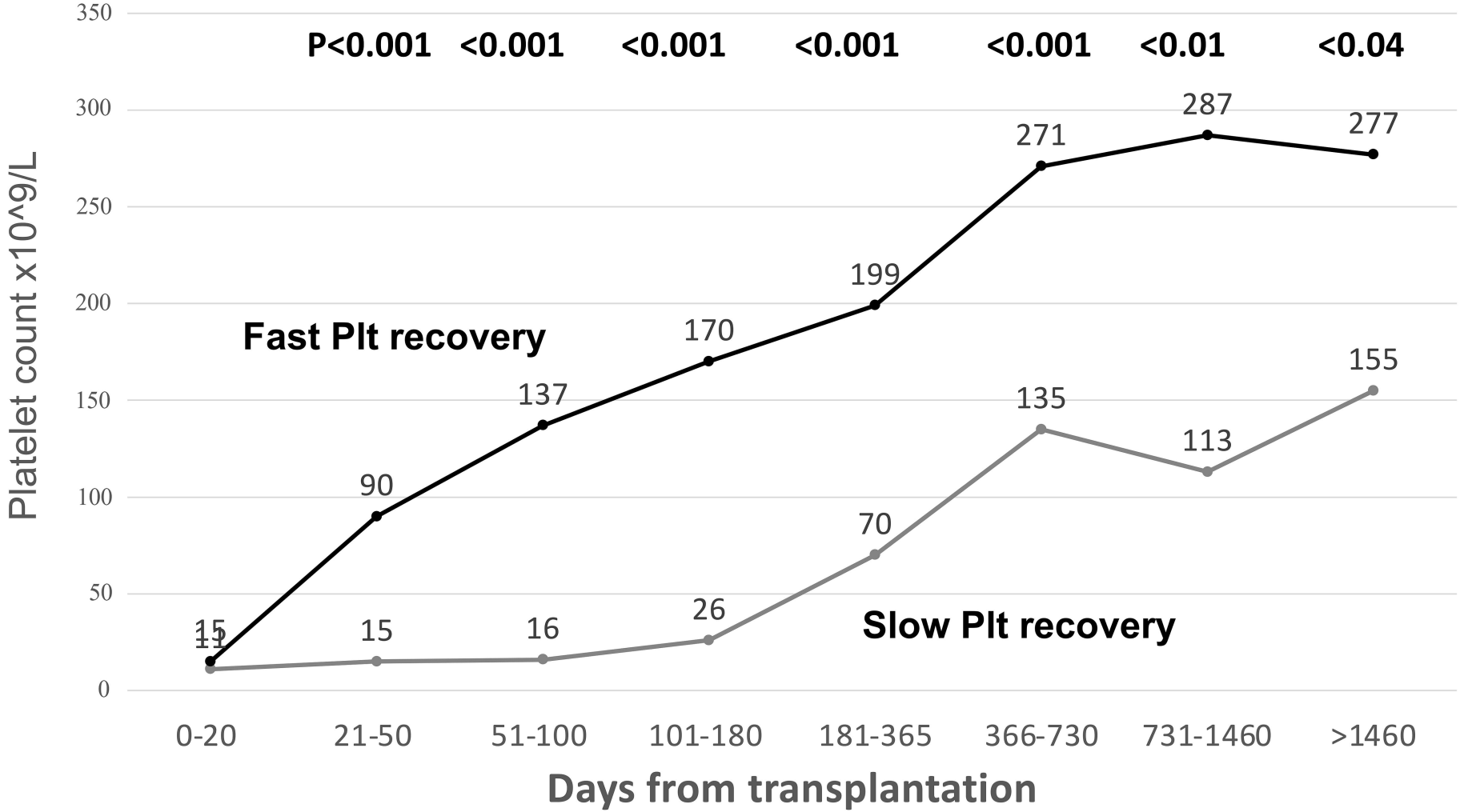

b
Overall survival
100%
80%
60%
40%
20%
0%
% surviving
0-1 adverse fact; n=32
90%
2 adverse fact; n=45
60%
42%
3 adverse fact; n=16
P=0.0006
0
1
2
3
4
5
years from transplant

Fig.3


P<0.001
<0.001
<0.001
<0.001
<0.001
<0.01
<0.04
Platelet count x10^9/L
350
300
250
200
150
100
50
0
Fast Plt recovery
Slow Plt recovery
15
90
137
170
199
271
287
277
11
15
16
26
70
135
113
155
0-20
21-50
51-100
101-180
181-365
366-730
731-1460
>1460
Days from transplantation