Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods

Effect of changing parity of female blood donors

In a further analysis which was restricted to the SCANDAT cohort, we utilized the long-standing and detailed parity data available in this database to perform an analysis investigating mortality outcomes of patients who had received red-cell transfusions from female donors who changed parity status. We first identified all female donors who had begun donating before having delivered their first child, and who had continued donating blood after that birth. We then tracked all their recipients and performed a survival analysis by following each of these recipients from the time of transfusion until death or end of follow-up. Patients who had received a blood unit from more than one such donor was thus included in the analysis more than once. The analyses were then conducted using Cox regression run in two sequential steps. We first fitted a survival model incorporating calendar year (as a categorical term), hospital (as a categorical term), patient age (as a restricted cubic term with 3 equally placed knots), and patient sex (as a categorical term). We then extracted the log-linear predictor estimated from the first model, and used this as an offset in a second stratified Cox model where we incorporated donor parity status (nulliparous, 1 pregnancy, 2 pregnancies, or ≥3 pregnancies), and where each donor constituted a separate stratum, whereby comparisons were only done between multiple recipients of the same donor. These analyses were conducted in two steps to allow careful adjustment first for factors that often change only rarely for a given donor (i.e. hospital), or factors where the effect would be hard to disentangle from the effect of parity (i.e. calendar year as parity can only increase). The two-step approach would then effectively treat factors considered in the first model to be derived from

between cluster comparisons and donor parity would only be assessed within each cluster, i.e. comparing all recipients of each donor. In effect, this means that the analyses were adjusted for all constant donor-specific factors (e.g. blood group or erythrocyte surface antigens) that might be involved in the selection of a particular blood unit for a particular patient, and which might otherwise confound the association between donor characteristics and patient outcomes. Because a recipient who received a blood unit from more than one female donor with a changing parity status would be included in this analysis as more than one observation, confidence intervals were constructed using a bootstrap approach with 10,000 runs.[1] In addition, we also performed analyses where the second step was omitted and where donor parity was included instead in the first model to provide estimates that were not adjusted for unmeasured donor factors.

Analyses investigating effect of discharge from hospital as a competing risk

Because discharge from hospital might constitute a competing event in the in-hospital mortality analyses, we performed sensitivity analyses investigating whether analyses accounting for such competing risks using a Fine-Gray model produced different results.[2] Because the Fine-Gray model implementation in the PHREG procedure in the SAS Statistical Analysis package doesn't allow the use of stratifying variables when set up for the Andersen-Gill counting process, we opted for adjusting for the three stratifying variables instead; hospital as a categorical term, calendar year as a categorical term, and number of red-cell transfusions as a restricted cubic spline with 5 manually placed knots. To avoid influence of scarce data among the few patients with very large numbers of transfusions, which could result in insufficient statistical adjustment, we restricted the

analyses to patients who received a maximum of 50 transfusions. Also, for reasons of computational demands, we were not able to run these analyses using the full SCANDAT database. Instead these sensitivity analyses were conducted on a random sample of 10% of patients in the database.

For each site, we ran analyses for each of the three exposure variables, expressed as linear terms, one with the standard Cox model and one with the Fine-Gray model. As is evident from eTable 6, below, results were very similar. The choice of presenting results derived using the stratified Cox models was thus deemed to be justified as those models could be run using the full SCANDAT dataset.

eTable 1. Effect of Association Between Donor Parameters on Recipient Mortality Upon Adding Additional Parameters As Stratification Variables in the Cox Model, to Account for Possible Non-Proportional Hazards*

	Number of transfusions from female donors	**Number of transfusions from parous female donors**	**Number of sex-discordant transfusion**
Kaiser-Permanente Northern California	*Hazard ratio (95% confidence interval)*		
Stratified by hospital, calendar year and number of transfusions	1.01 (1.00-1.01)	0.99 (0.98-1.01)	1.01 (1.00-1.02)
Stratified by hospital, calendar year, number of transfusions and recipient sex	1.00 (0.98-1.03)	1.00 (0.98-1.01)	1.01 (0.99-1.03)
REDS-III			
Stratified by hospital, calendar year and number of transfusions	1.01 (0.98-1.03)	1.00 (0.98-1.02)	0.99 (0.98-1.01)
Stratified by hospital, calendar year, number of transfusions and recipient sex	1.02 (0.99-1.05)	1.00 (0.98-1.03)	0.99 (0.97-1.01)
Stratified by hospital, calendar year, number of transfusions, recipient sex and recipient blood group	1.00 (0.98-1.03)	1.00 (0.97-1.02)	0.99 (0.98-1.01)
Stratified by hospital, calendar year, number of transfusions, recipient sex, recipient blood group, and Charlson index	1.02 (0.98-1.05)	1.00 (0.97-1.03)	0.99 (0.97-1.01)
SCANDAT			
Stratified by hospital, calendar year and number of transfusions	1.00 (0.99-1.00)	1.00 (1.00-1.01)	1.00 (0.99-1.00)
Stratified by hospital, calendar year, number of transfusions and recipient sex	1.00 (0.99-1.00)	1.00 (1.00-1.01)	1.00 (1.00-1.00)

Stratified by hospital, calendar year, number of transfusions, recipient sex and recipient blood group	1.00 (0.99-1.00)	1.00 (1.00-1.01)	1.00 (1.00-1.00)
Stratified by hospital, calendar year, number of transfusions, recipient sex, recipient blood group, and Charlson index	1.00 (0.99-1.00)	1.00 (1.00-1.01)	1.00 (1.00-1.01)

*Estimates were derived by successively adding more parameters as stratification variables in the models. Hazard ratio estimates do not fully match estimates in Table 2 as the proportional hazards testing models were not run with multiple imputation (KPNC and REDS-III).

eTable 2. Unadjusted Mortality Rates, in Relation to Number of Transfused Sex-Discordant Units, Units From Female Donors, and Units From Previously Pregnant Donors, Estimated From In-Hospital Mortality Analyses

	Number of units of each risk category				
	None	1-2	3-4	5-6	≥7
Kaiser-Permanente Northern California	*Mortality rate per 1,000 person-years*				
Number of transfusions from female donors	2966	3249	4485	5879	9050
Number of transfusions from parous female donors	3385	3827	4831	5608	8565
Number of sex-discordant transfusions	2879	3225	4665	5534	8181
REDS-III					
Number of transfusions from female donors	2385	2542	2879	3345	4486
Number of transfusions from parous female donors	2642	2805	3377	3796	6581
Number of sex-discordant transfusions	1857	2487	3107	3384	5404
SCANDAT					
Number of transfusions from female donors	490	451	493	566	657
Number of transfusions from parous female donors†	473	464	535	632	704
Number of sex-discordant transfusions	479	450	491	558	657

eTable 3. Unadjusted Mortality Rates, in Relation to Number of Transfused Sex-Discordant Units, Units From Female Donors, and Units From Previously Pregnant Donors, Estimated From Long-Term Mortality Analyses

	Number of units of each risk category				
	None	1-2	3-4	5-6	≥7
Kaiser-Permanente Northern California	*Mortality rate per 1,000 person-years*				
Number of transfusions from female donors	159	163	228	317	431
Number of transfusions from parous female donors	169	208	310	365	317
Number of sex-discordant transfusions	154	164	219	299	426
SCANDAT					
Number of transfusions from female donors	116	134	197	259	342
Number of transfusions from parous female donors†	121	152	240	312	397
Number of sex-discordant transfusions	123	319	175	233	320

eTable 4. Results From Analyses Investigating the Effect of Donor Sex and Parity on Patient Survival Based on Single Unit Cohort

	No. patients	**No. deaths**	**Mortality rate/ 1,000 person-years**	**Hazard ratio (95% confidence interval)***
All recipients				
Male donor	137 130	12 882	286	1.00 (ref)
Nulliparous female donor	36 582	3 221	281	0.96 (0.93-1.00)
Parous female donor	55 972	4 919	293	0.97 (0.94-1.01)
Male recipients, age <50 years				
Male donor	9 006	312	78	1.00 (ref)
Nulliparous female donor	2 504	93	89	0.85 (0.64-1.14)
Parous female donor	3 627	152	103	0.95 (0.74-1.23)

*Hazard ratios were calculated using standard Cox regression adjusted for patient age, sex, and Charlson comorbidity index, as well as hospital and year of transfusion, each constituting separate strata in the model.

eTable 5. Results From Analyses Investigating the Effect of Donor Sex and Parity on Patient Survival Based on Discrete Exposure Group Cohort

	No. patients	**No. Deaths**	**Mortality rate/ 1,000 person-years**	**Hazard Ratio (95% confidence interval)***
All recipients				
Male donor(s)	355 655	40 407	270	1.00 (ref)
Nulliparous female donor(s)	52 318	5 111	275	0.98 (0.95-1.01)
Parous female donor (s)	90 891	9 199	284	0.99 (0.97-1.01)
Male recipients, age <50 years				
Male donor(s)	17 700	693	85	1.00 (ref)
Nulliparous female donor(s)	3 212	123	89	0.92 (0.72-1.17)
Parous female donor (s)	4 969	213	102	1.00 (0.81-1.23)

†Hazard ratios were calculated using standard Cox regression adjusted for patient age, sex, number of transfusions, and Charlson comorbidity index, as well as hospital and year of transfusion, each constituting separate strata in the model.

eTable 6. Comparison of Standard Cox Model and Fine-Gray Model for Analyses of In-Hospital Mortality.

	Model 1: Stratified Cox model*		**Model 2: Standard Cox model†**		**Model 3: Fine-Gray model****
Kaiser-Permanente Northern California	*Hazard ratio per unit transfused (95% confidence interval)*				
Number of transfusions from female donors	1.00 (0.98-1.03)		1.00 (1.00-1.01)		1.00 (1.00-1.01)
Number of transfusions from parous female donors	1.00 (0.96-1.04)		1.00 (0.99-1.00)		1.00 (0.99-1.00)
Number of sex-discordant transfusion	1.01 (0.99-1.04)		1.01 (1.01-1.02)		1.01 (1.00-1.02)
REDS-III					
Number of transfusions from female donors	1.00 (0.98-1.02)		1.01 (0.99-1.03)		1.01 (0.99-1.03)
Number of transfusions from parous female donors	1.01 (0.98-1.04)		1.02 (0.99-1.04)		1.02 (1.00-1.04)
Number of sex-discordant transfusion	0.99 (0.98-1.01)		1.01 (0.99-1.04)		0.99 (0.98-1.01)
SCANDAT††					
Number of transfusions from female donors	1.01 (0.99-1.02)		1.00 (0.99-1.02)		1.00 (0.99-1.01)
Number of transfusions from parous female donors	1.01 (0.99-1.02)		1.00 (0.99-1.02)		1.00 (0.99-1.01)
Number of sex-discordant transfusion	1.00 (0.99-1.02)		1.00 (0.99-1.01)		1.00 (0.99-1.01)

*Using a stratified Cox model. Identical to model used in Table 2 of the main manuscript.

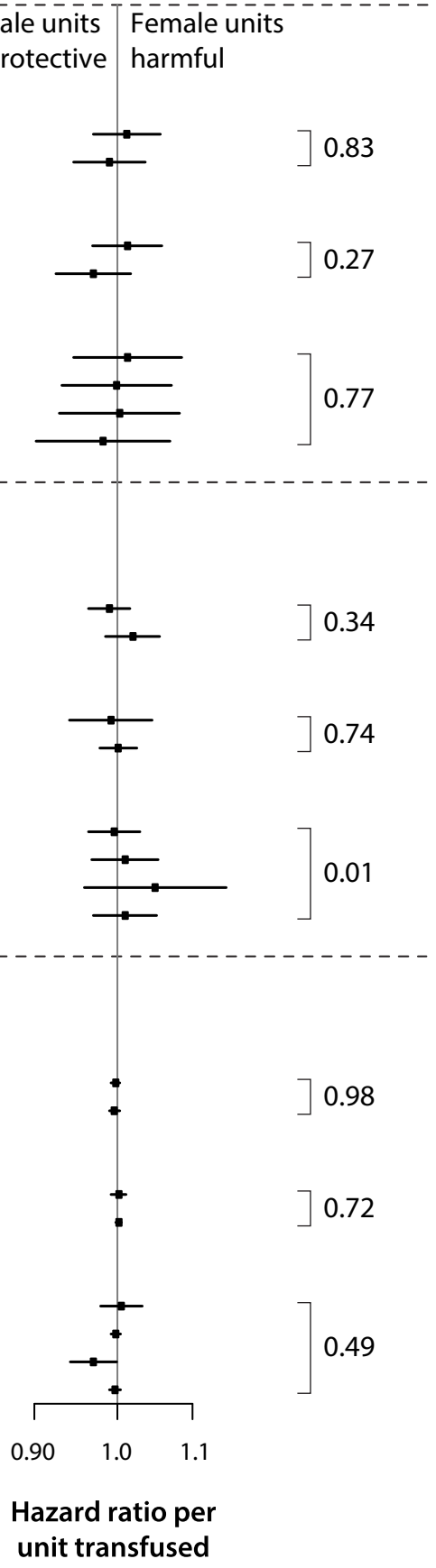
†Using a standard Cox model identical to Model 1, but with adjustment instead of stratifying for hospital, year and number of transfusions.

**Identical to Model 2, but treating discharge from hospital as a competing event.

††For computational reasons, these analyses were based on random sample of 10% of SCANDAT data.

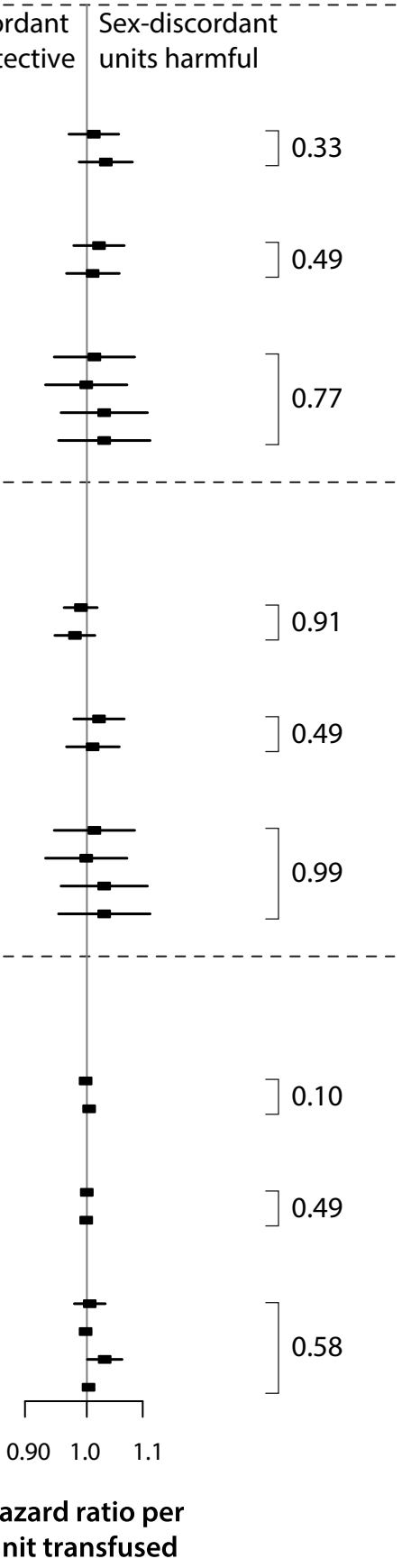
eFigure 1 - Subgroup analyses for number of red-cell units from female donors

Patient group	Number of deaths/ patient episodes	Hazard ratio per unit transfused*	*P* for interaction**
KPNC			
Recipient sex			
Male	1,719/21,666	1.01 (0.97–1.06)	0.83
Female	1,498/24,424	0.99 (0.95–1.04)	
Recipient age			
<50 years	323/5,514	1.01 (0.97–1.06)	0.27
≥50 years	2,894/40,576	0.97 (0.92–1.02)	
Recipient sex			
Male, <50 years	171/2,335	1.01 (0.95–1.08)	0.77
Male, ≥50 years	1,548/19,331	1.00 (0.93–1.07)	
Female, <50 years	152/3,179	1.00 (0.93–1.08)	
Female, ≥50 years	1,346/21,245	0.98 (0.90–1.07)	
REDS-III			
Recipient sex			
Male	5,146/63,373	0.99 (0.96–1.02)	0.34
Female	4,168/66,746	1.02 (0.99–1.06)	
Recipient age			
<50 years	1,728/31,490	0.99 (0.94–1.04)	0.74
≥50 years	7,586/98,629	1.00 (0.98–1.02)	
Recipient sex			
Male, <50 years	986/14,545	1.00 (0.96–1.03)	0.01
Male, ≥50 years	4,160/48,828	1.01 (0.97–1.05)	
Female, <50 years	742/16,945	1.05 (0.96–1.15)	
Female, ≥50 years	3,426/49,801	1.01 (0.97–1.05)	
SCANDAT			
Recipient sex			
Male	105,891/593,544	1.00 (0.99–1.00)	0.98
Female	94,752/748,496	1.00 (0.99–1.00)	
Recipient age			
<50 years	13,652/192,041	1.00 (0.99–1.01)	0.72
≥50 years	186,991/1,149,999	1.00 (1.00–1.01)	
Recipient sex			
Male, <50 years	7,044/68,314	1.00 (0.98–1.03)	0.49
Male, ≥50 years	98,847/525,230	1.00 (0.99–1.00)	
Female, <50 years	6,608/123,727	0.97 (0.94–1.00)	
Female, ≥50 years	88,144/624,769	1.00 (0.99–1.00)	



eFigure 2 - Subgroup analyses for number of sex-discordant red-cell units

Patient group	Number of deaths/ patient episodes	Hazard ratio per unit transfused*	*P* for interaction**
KPNC			
Recipient sex			
Male	1,719/21,666	1.01 (0.97–1.06)	0.33
Female	1,498/24,424	1.03 (0.99–1.08)	
Recipient age			
<50 years	323/5,514	1.02 (0.98–1.07)	0.49
≥50 years	2,894/40,576	1.01 (0.97–1.06)	
Recipient sex			
Male, <50 years	171/2,335	1.01 (0.95–1.08)	0.77
Male, ≥50 years	1,548/19,331	1.00 (0.93–1.07)	
Female, <50 years	152/3,179	1.03 (0.96–1.11)	
Female, ≥50 years	1,346/21,245	1.03 (0.95–1.11)	
REDS-III			
Recipient sex			
Male	5,146/63,373	0.99 (0.96–1.02)	0.91
Female	4,168/66,746	0.98 (0.95–1.01)	
Recipient age			
<50 years	1,728/31,490	1.02 (0.98–1.07)	0.49
≥50 years	7,586/98,629	1.01 (0.97–1.06)	
Recipient sex			
Male, <50 years	986/14,545	1.01 (0.95–1.08)	0.99
Male, ≥50 years	4,160/48,828	1.00 (0.93–1.07)	
Female, <50 years	742/16,945	1.03 (0.96–1.11)	
Female, ≥50 years	3,426/49,801	1.03 (0.95–1.11)	
SCANDAT			
Recipient sex			
Male	105,891/593,544	1.00 (0.99–1.00)	0.10
Female	94,752/748,496	1.00 (1.00–1.01)	
Recipient age			
<50 years	13,652/192,041	1.00 (0.99–1.01)	0.49
≥50 years	186,991/1,149,999	1.00 (1.00–1.00)	
Recipient sex			
Male, <50 years	7,044/68,314	1.01 (0.98–1.03)	0.58
Male, ≥50 years	98,847/525,230	1.00 (0.99–1.00)	
Female, <50 years	6,608/123,727	1.03 (1.00–1.06)	
Female, ≥50 years	88,144/624,769	1.00 (1.00–1.01)	



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2. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; **94**(446): 496-509.