SUPPLEMENTARY APPENDIX

Transfusion of packed red blood cells at the end of shelf life is associated with increased risk of mortality – a pooled patient data analysis of 16 observational trials

Monica S.Y. Ng,[1,2] Michael David,[3] Rutger A. Middelburg,[4,5] Angela S.Y. Ng,[1] Jacky Y. Suen,[1] John-Paul Tung[1,2] and John F. Fraser[1]

[1]Critical Care Research Group, Faculty of Medicine, University of Queensland, Brisbane, Australia; [2]Research and Development, Australian Red Cross Blood Service, Brisbane, Australia; [3]School of Medicine and Population Health, The University of Newcastle, Callaghan, Australia; [4]Centre for Clinical Transfusion Research, Sanquin Research, Leiden, the Netherlands and [5]Department of Clinical Epidemiology, Leiden University Medical Center, the Netherlands

 doi:10.3324/haematol.2018.191932

Received: February 22, 2018.

Accepted: May 21, 2018.

Pre-published: May 24, 2018.

Correspondence: monica.ng91@gmail.com

Supplementary 1: Comparison of studies for which individual dataset were available compared to studies where individual datasets were unavailable

Study features	**Available** (n=16)	**Unavailable** (n=40)
Recruitment year[1] (count, %)		
1980-1989	2 (12.50)	0 (0.00)
1990-1999	2 (12.50)	10 (25.00)
2000-2009	11 (68.75)	25 (62.50)
2010-2019	1 (6.25)	5 (12.50)
Not reported	0 (0.00)	5 (12.50)
Location (count, %)		
Europe	9 (56.25)	10 (25.00)
Americas	4 (25.00)	28 (70.00)
Asia + Oceania	2 (12.5)	2 (2.00)
Other	1 (6.25)	0 (0.00)
Sample size (mean, SD)	904.56 (297.44)	1003.53 (254.83)[2]
Clinical subgroup (count, %)		
Cardiac surgery	4 (25.00)	10 (25.00)
Intensive care unit	5 (31.25)	5 (12.50)
General surgery	2 (12.50)	6 (15.00)
Acute medicine	1 (6.25)	3 (7.50)
Orthopedic surgery	1 (6.25)	2 (5.00)
Trauma	1 (6.25)	13 (32.50)
Other	2 (12.50)	1 (2.50)
Rate of positive findings[3] (count, %)		
Mortality	4/16 (36.36)	8/24 (33.33)
Nosocomial infection	1/8 (12.50)	9/16 (56.25)
Hospital length of stay	1/4 (25.00)	3/7 (42.86)

Abbreviations: SD=standard deviation
[1] First year of recruitment
[2]Population level study with n=404,959 excluded from calculation
[3]Positive findings = association between packed red blood cell storage duration and clinical outcome; % expressed as: number of studies with positive findings/number of studies reporting outcome x 100%

Supplementary 2: Demographic variables available for aggregate dataset by study

Paper	Source	Country	Sample size	Recruitment period	Age	Gender	Smoker	Dyslipidaemia	Hypertension	Diabetes mellitus	Lung disease	CKD	CLD	ChemoRTx	Vascular disease	BMI	Malignancy	Heart failure	EF	ASA score	APACHE
Cartotto 2011 (1)	Burns	CAN	127	1 Apr 2000- 1Apr 2010																	
Edna 1994 (2)	Biliary surgery	NOR	84	1 Jan 1980- 31 Dec 1990																	
Edna 1998 (3)	Colorectal cancer	NOR	328	1 Jan 1980-31 Dec 1992																5	
Gajic 2004 (4)	ICU PMV	USA	172	1 Jan 2001- 31 Dec 2001																	
Juffermans 2011 (5)	ICU septic	NLD	65	1 Jan 2004- 30 Nov 2007																	
Juffermans 2012 (6)	ICU trauma	NLD	192	1 Jan 2004- 30 Nov 2007																	1
Kadar 2013 (7)	#Hip surgery	ISR	871	1 Jan 2007- 21 Dec 2010																297	
Kaukonen 2013 (8)	ICU	FIN	652	1 Sep 2011- 30 Nov 2011												5			503		
Kekre 2013 (9)	Oncology	CAN	2296	1 Jan 2000- 31 Dec 2005																	
Middelburg 2013 (10)	Acute medicine	NLD	7621	1 Jan 2005- 31 May 2009																	
Petilla 2011 (11)	ICU	ANZ	757	1 Aug 2008- 20 Sep 2008																	
Phelan 2010 (12)	Trauma	USA	399	19 months																	
Sanders 2011 (13)	Cardiac surgery	GBR	183	1 Jan 2005- 30 Nov 2007												12					
Van de Watering 2006 (14)	Cardiac surgery	NLD	2729	1 Jan 1993- 31 Dec 1999																	
Voorhuis 2013 (15)	Cardiac surgery	NLD	821	1 Sep 2006- 31 Dec 2010																	
Yap 2008 (16)	Cardiac surgery	ANZ	670	1 Jun 2001- 31 Jul 2007			262														

Abbreviations: #Hip: hip fracture, ANZ: Australia and New Zealand, APACHE: Acute Physiology and Chronic Health Evaluation score, ASA: American Society of Anaesthesiologists score, BMI: body mass index, CAN: Canada, ChemoRtx: chemoradiotherapy, CKD: chronic kidney disease, CLD: chronic liver disease, EF: ejection fracture: FIN: Finland, GBR: United Kingdom, ICU: intensive care unit, ISR: Israel, NLD: Netherlands, NOR: Norway, PMV: prolonged mechanical ventilation (>48hours), USA: United States of America
Key: green shading: data available, white shading: data not available, numbers: number of missing values

Supplementary 3: Transfusion data available for aggregate dataset by study

Paper	PRBC volume	Age of each PRBC unit	PRBC mean	PRBC max	PRBC min	PRBC old	PC volume	Age of each PC unit	PC mean	FFP volume	Age of each FFP unit	FFP mean	ABO status
Cartotto 2011 (1)													
Edna 1994 (2)													
Edna 1998 (3)													
Gajic 2004 (4)				1			28						
Juffermans 2011 (5)													
Juffermans 2012 (6)													
Kadar 2013 (7)	1							4	4		5	5	
Kaukonen 2013 (8)													
Kekre 2013 (9)													
Middelburg 2013 (10)									3	3			461
Petilla 2011 (11)	2							5		4	4		
Phelan 2010 (12)													
Sanders 2011 (13)													
Van de Watering 2006 (14)	2												450
Voorhuis 2013 (15)													
Yap 2008 (16)													

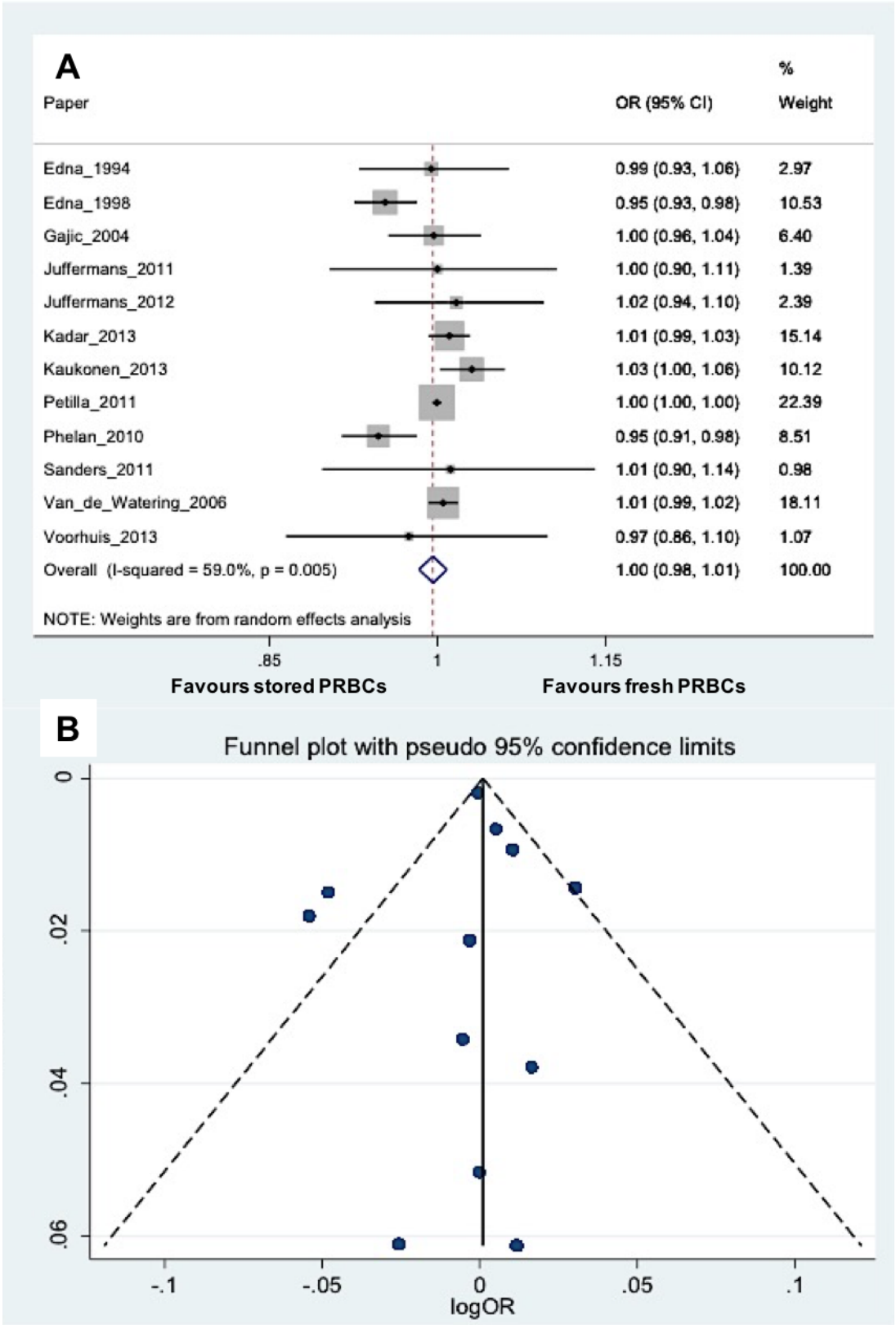
Abbreviations: FFP: fresh frozen plasma, PC: platelet concentrate, PRBC: packed red blood cells, PRBC old: whether PRBC mean <14 days old
Key: green shading: data available, white shading: data not available, numbers: number of missing values
NB: PRBC mean, PRBC max, PRBC min and PRBC old can be derived from age of each PRBC unit

Supplementary 4: Outcome data available for aggregate dataset by study

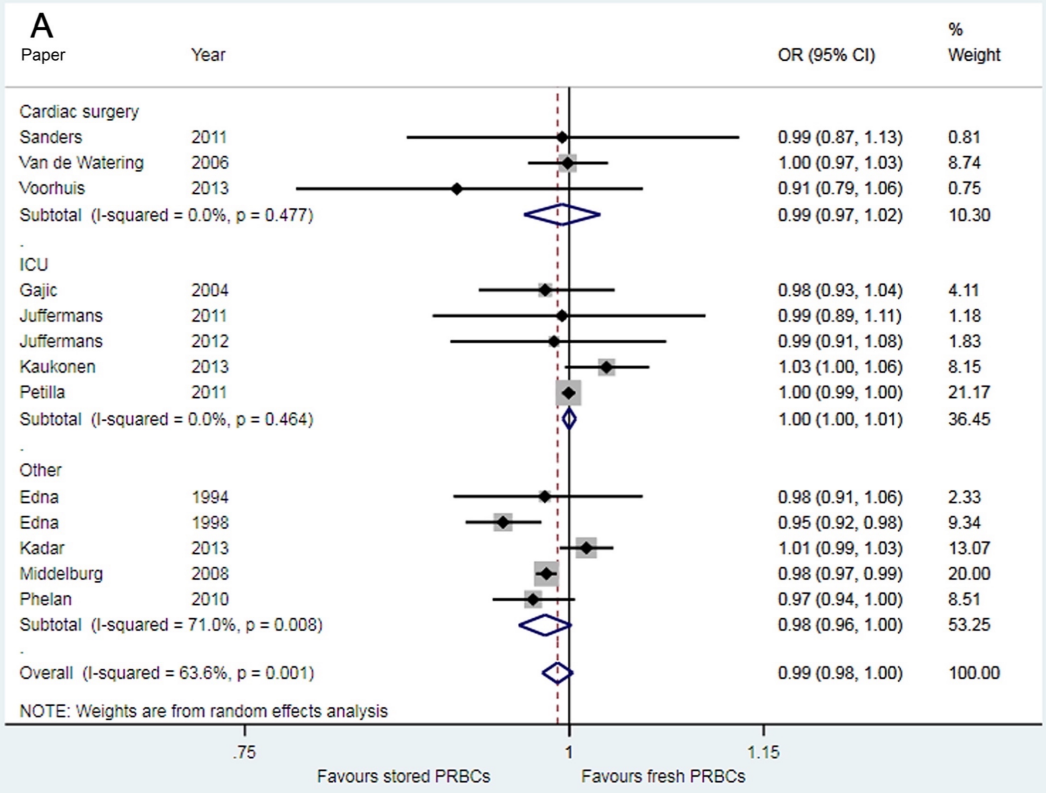
Paper	Mortality	HLOS	ILOS	Pneumonia	Wound infection	UTI	BSI	Other infection	Any infections	Sepsis	MV duration	Renal failure	MI	Neurological deficit	MOF
Cartotto 2011 (1)															
Edna 1994 (2)															
Edna 1998 (3)															
Gajic 2004 (4)		7								3					
Juffermans 2011 (5)															
Juffermans 2012 (6)															
Kadar 2013 (7)															
Kaukonen 2013 (8)		1													
Kekre 2013 (9)	2														
Middelburg 2013 (10)	1														
Petilla 2011 (11)		189													
Phelan 2010 (12)															
Sanders 2011 (13)															
Van de Watering 2006 (14)	16														
Voorhuis 2013 (15)															
Yap 2008 (16)	1														

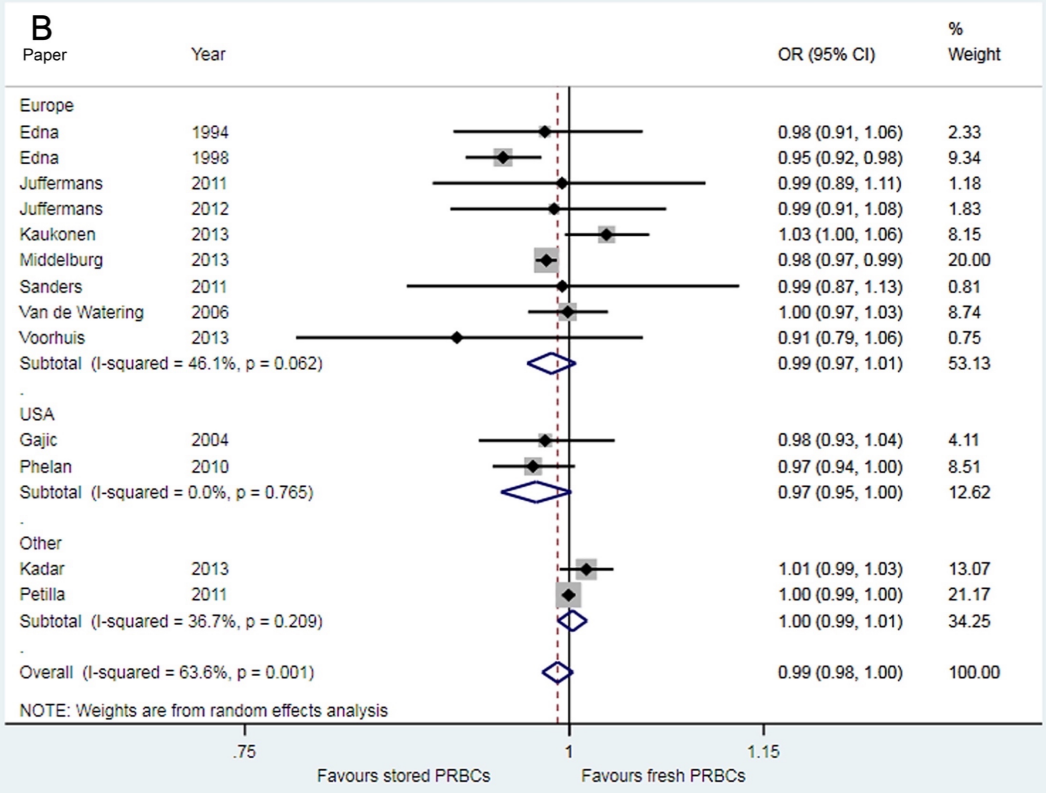
Abbreviations: BSI: bloodstream infection, HLOS: hospital length of stay, ILOS: intensive care unit length of stay, MI: myocardial infarction, MOF: multiple organ failure, MV: mechanical ventilation, UTI: urinary tract infection,
Key: green shading: data available, white shading: data not available, numbers: number of missing values

Supplementary 5: Forest plots and funnel plots for mortality analysis as a function of maximum PRBC age. Mortality odds ratios were calculated for each study using logistic regression with maximum PRBC age transfused as the independent variable. Age, gender and PRBC volume were covariates. Odds ratios were combined using random effects models (A). Funnel plots were generated for each analyses to assess publication bias (B).

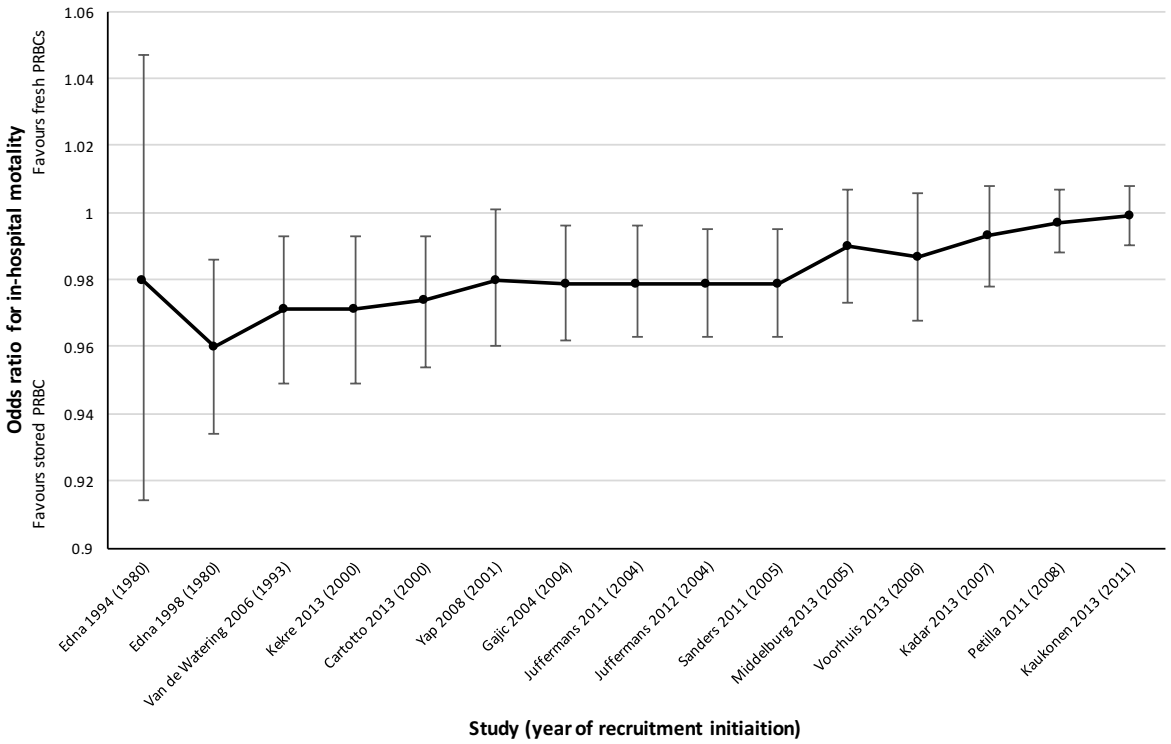


Supplementary 6: Subgroup analyses for in-hospital mortality as a function of mean PRBC age. Papers stratified by patient subgroup (A) and geographical location (B). ORs calculated for each paper using logistic regression adjusted for age, gender and PRBC volume.

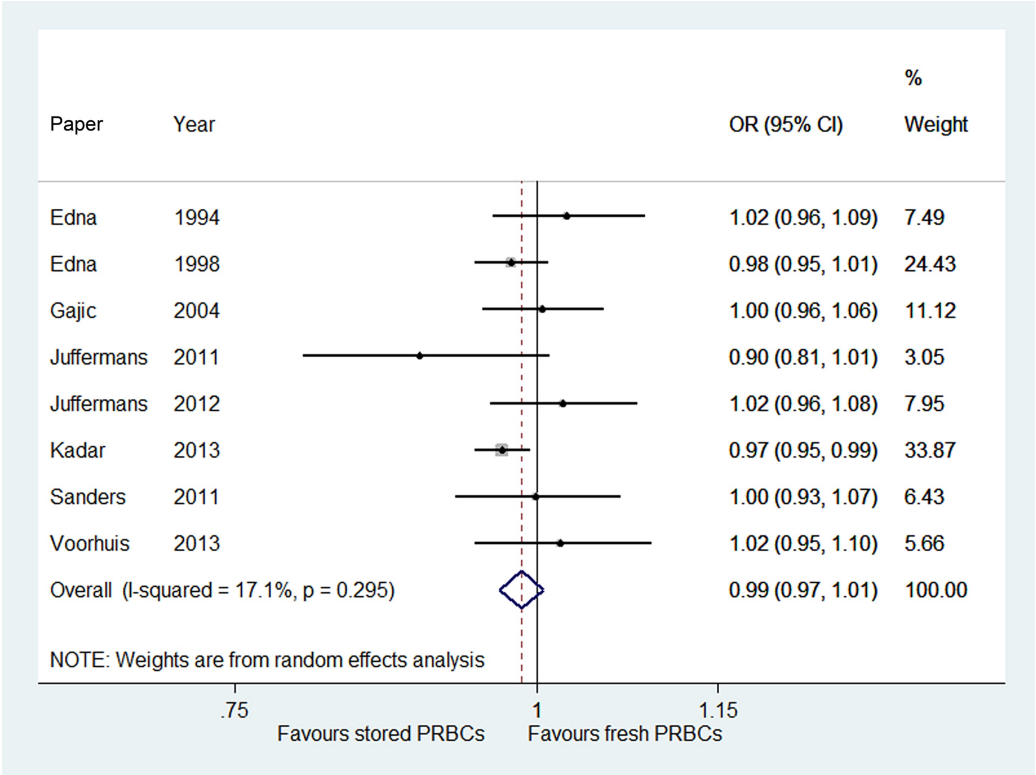




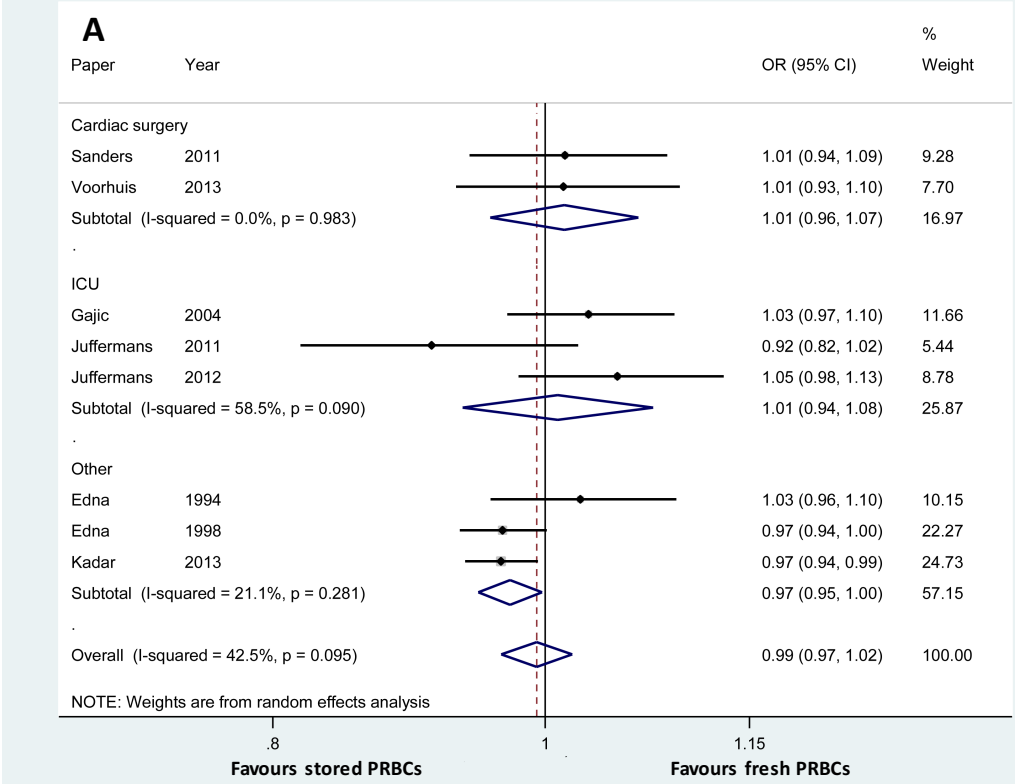
Supplementary 7: Time lapse analysis for in-hospital mortality as a function of mean PRBC age. Each study was incorporated into the random effects model in chronological order based on first year of recruitment initiation.

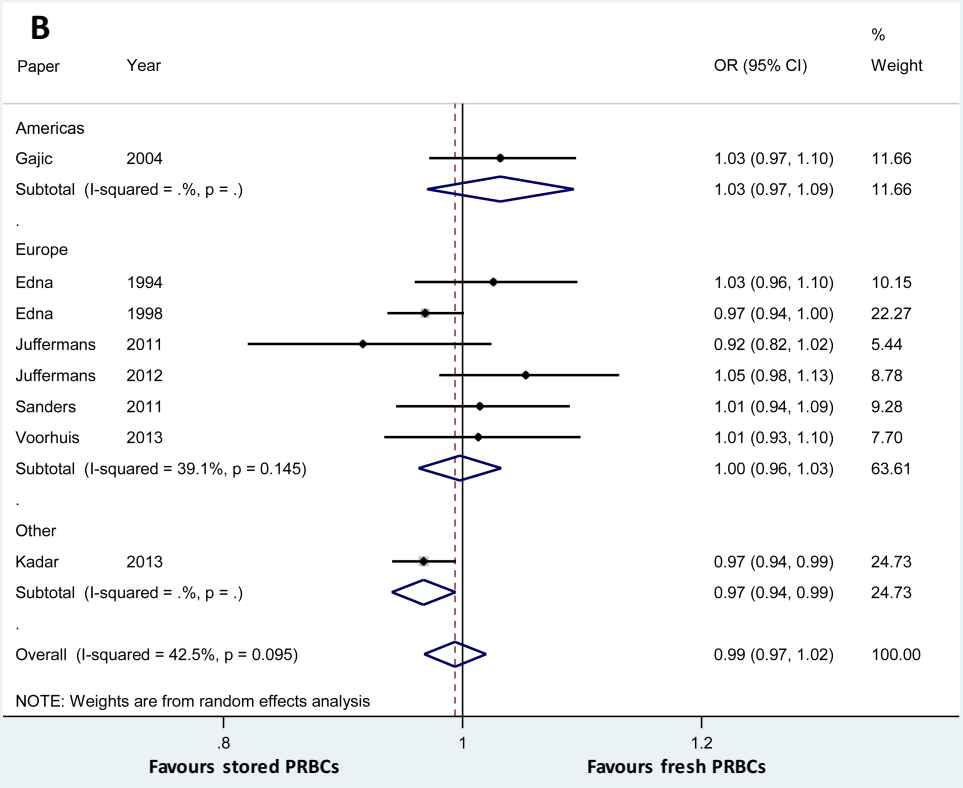


Supplementary 8: Forest plots for nosocomial infection analysis as a function of maximum PRBC age. Nosocomial infection odds ratios were calculated for each study using logistic regression with maximum PRBC age as the independent variable. Age, gender and PRBC volume were entered into the model as covariates. Odds ratios were then combined using random effects models.

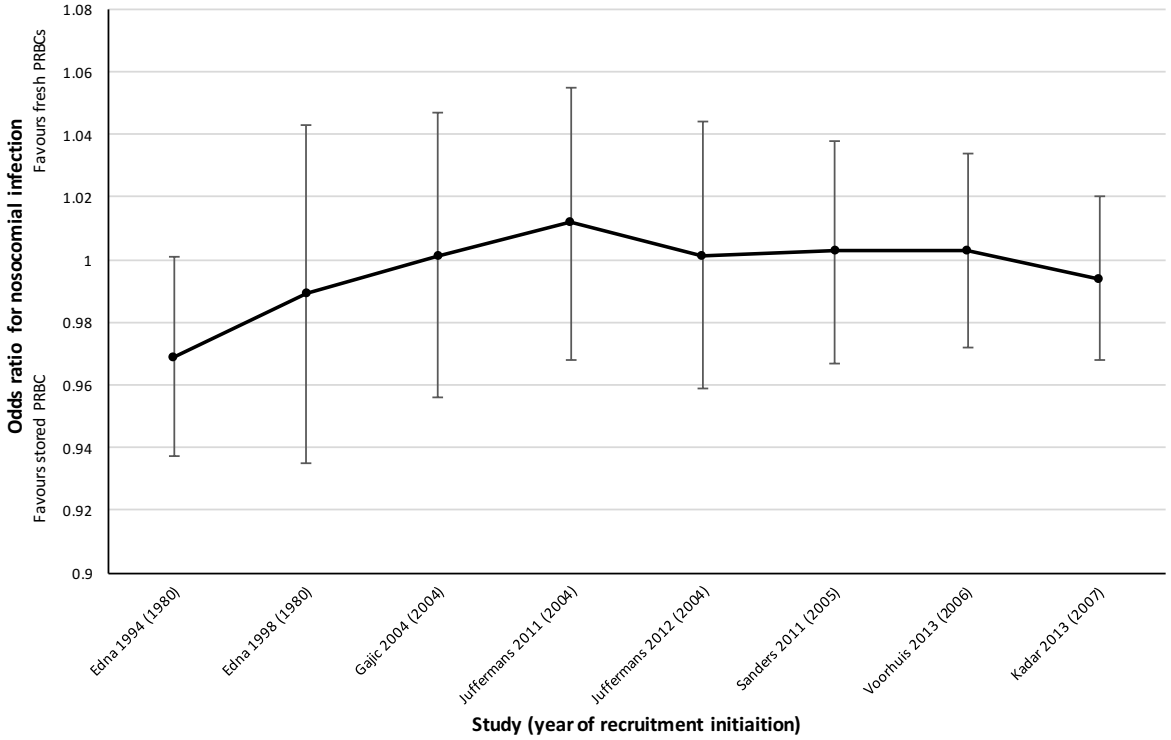


Supplementary 9: Subgroup analyses for nosocomial infection as a function of mean PRBC age. Papers stratified by patient subgroup (A) and geographical location (B). ORs calculated for each paper using logistic regression adjusted for age, gender and PRBC volume.

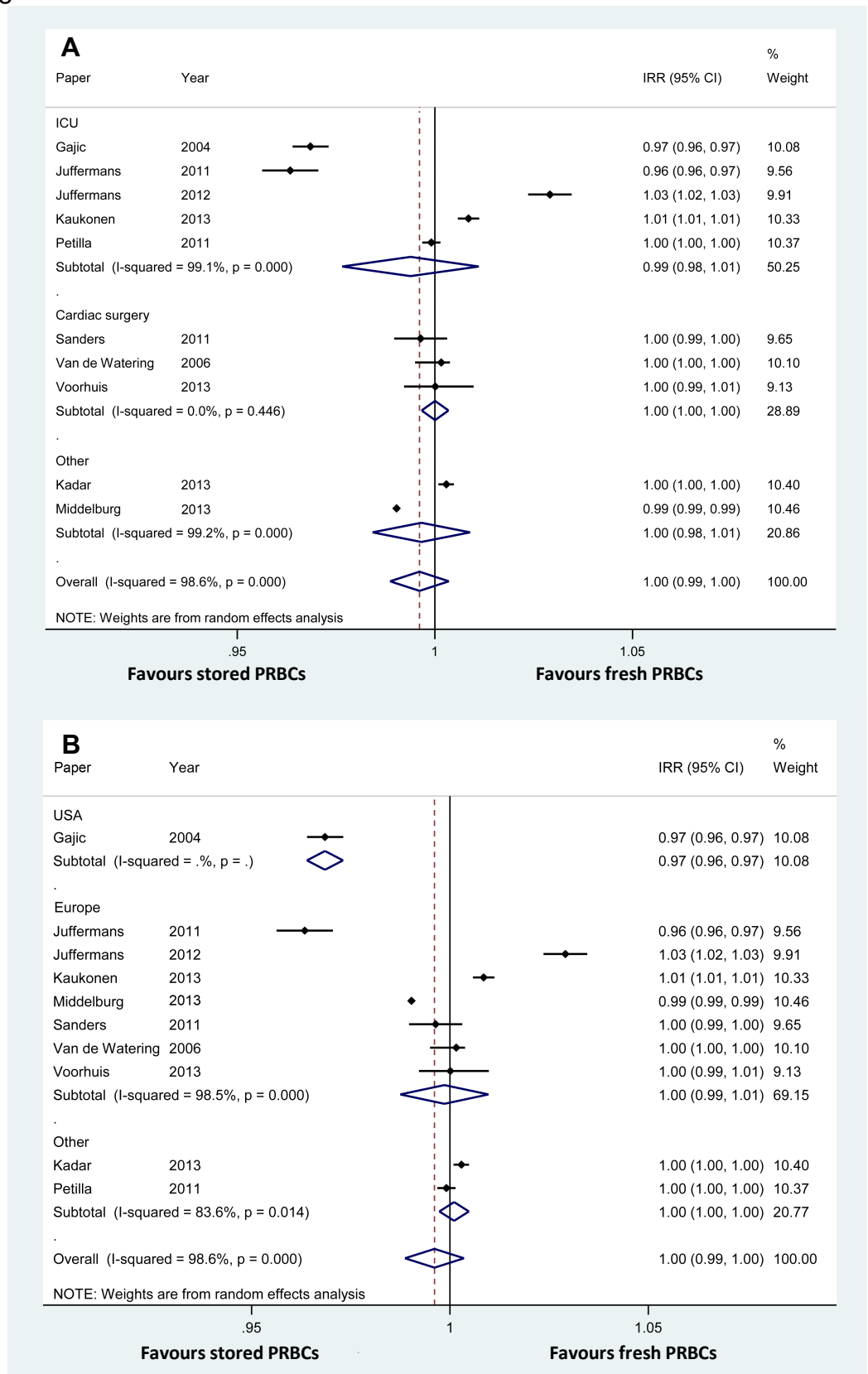




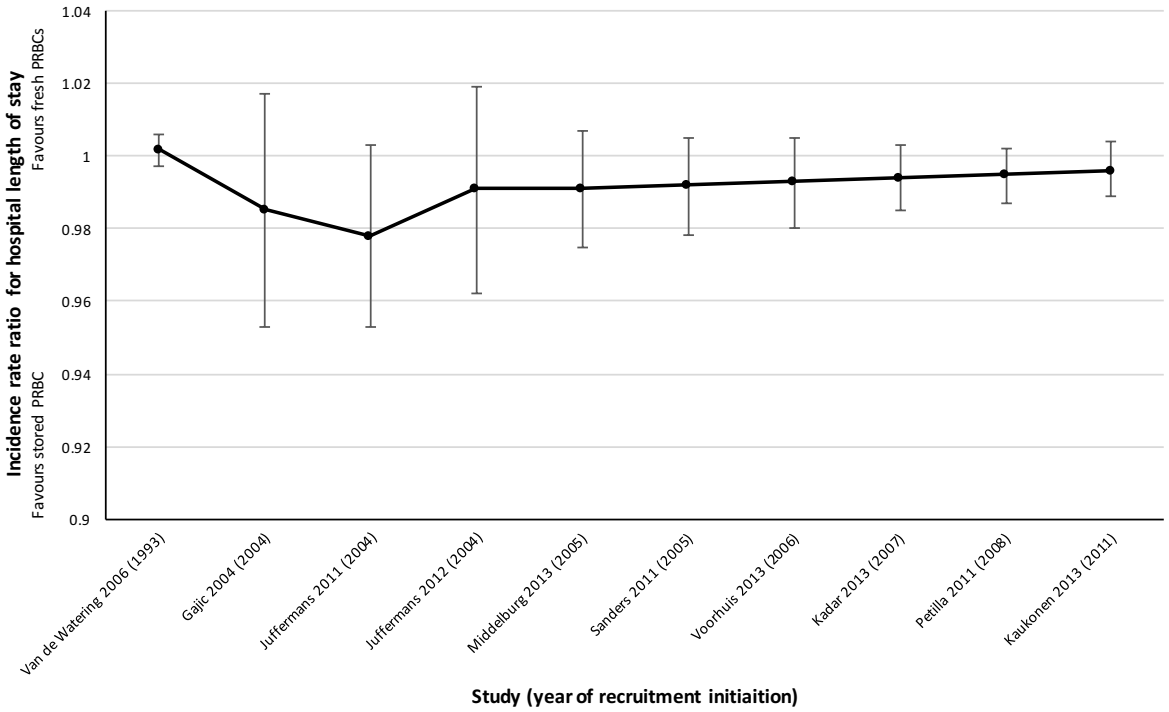
Supplementary 10: Time lapse analysis for nosocomial infection as a function of mean PRBC age. Each study was incorporated into the random effects model in chronological order based on first year of recruitment initiation.



Supplementary 11: Subgroup analyses for hospital length of stay as a function of mean PRBC age. Papers stratified by patient subgroup (A) and geographical location (B). ORs calculated for each paper using logistic regression adjusted for age, gender and PRBC volume.



Supplementary 12: Time lapse analysis for hospital length of stay as a function of mean PRBC age. Each study was incorporated into the random effects model in chronological order based on first year of recruitment initiation.



References

1. Cartotto R, Yeo C, Camacho F, Callum J. Does the storage age of transfused blood affect outcome in burn patients? J Burn Care Res. 2013;24.
2. Edna TH, Bjerkeset T, Svinsås M, Drogset JO, Skreden K. Association between transfusion of stored blood and bacterial infective complications after biliary operations. Eur J Surg. 1994;160(6-7):357-362.
3. Edna TH, Bjerkeset T. Association between transfusion of stored blood and infective bacterial complications after resection for colorectal cancer. Eur J Surg. 1998;164(6):449-456.
4. Gajic O, Rana R, Mendez JL, et al. Acute lung injury after blood transfusion in mechanically ventilated patients. Transfusion. 2004;44(10):1468-1474.
5. Juffermans NP, Prins DJ, Vlaar AP, Nieuwland R, Binnekade JM. Transfusion-related risk of secondary bacterial infections in sepsis patients: a retrospective cohort study. Shock. 2011;35(4):355-359.
6. Juffermans NP, Vlaar AP, Prins DJ, Goslings JC, Binnekade JM. The age of red blood cells is associated with bacterial infections in critically ill trauma patients. Blood Transfus. 2012;10(3):290-295.
7. Kadar A, Chechik O, Katz E, et al. The effects of 'old' red blood cell transfusion on mortality and morbidity in elderly patients with hip fractures-A retrospective study. Injury. 2013;44(6):747-750.
8. Kaukonen KM, Vaara ST, Pettila V, et al. Age of red blood cells and outcome in acute kidney injury. Crit Care. 2013;17(5):R222.
9. Kekre N, Mallick R, Allan D, Tinmouth A, Tay J. The impact of prolonged storage of red blood cells on cancer survival. PloS one. 2013;8(7):e68820.
10. Middelburg RA, Van de Watering LMG, Briet E, Van der Bom JG. Storage time of red blood cells and mortality of transfusion recipients. Transfus Med Rev. 2013;27(1):36-43.
11. Pettila V, Westbrook AJ, Nichol AD, et al. Age of red blood cells and mortality in the critically ill. Crit Care. 2011;15(2).
12. Phelan HA, Gonzalez RP, Patel HD, et al. Prestorage leukoreduction ameliorates the effects of aging on banked blood. J Trauma. 2010;69(2):330-337.
13. Sanders J, Patel S, Cooper J, et al. Red blood cell storage is associated with length of stay and renal complications after cardiac surgery. Transfusion. 2011;51(11):2286-2294.
14. Van De Watering L, Lorinser J, Versteegh M, Westendord R, Brand A. Effects of storage time of red blood cell transfusions on the prognosis of coronary artery bypass graft patients. Transfusion. 2006;46(10):1712-1718.
15. Voorhuis FTR, Dieleman JM, De Vooght KMK, et al. Storage time of red blood cell concentrates and adverse outcomes after cardiac surgery: A cohort study. Ann Hematol. 2013;92(12):1701-1706.
16. Yap CH, Lau L, Krishnaswamy M, Gaskell M, Yii M. Age of Transfused Red Cells and Early Outcomes After Cardiac Surgery. Ann Thorac Surg. 2008;86(2):554-559.