SUPPLEMENTARY MATERIAL

Appendix 1.

The detailed search strategy is showed as follow:

PUBMED=317

1. ((((erythrocyte*) OR red cell*) OR red blood cell*) OR RBC*) OR blood
2. ((retransfus*) OR transfuse*) OR infuse*
3. ((((((((((*Time Factors) OR Blood Preservation) OR age*) OR aging) OR fresh*) OR old*) OR new*) OR young*) OR store*) OR storage) OR storing) OR preserv*
4. ((((((Critical Illness) OR Critical Care) OR Intensive Care) OR Intensive Care Units) OR Critically ill) OR Critical*) OR Intensive*
5. #1 AND #2 AND #3 AND #4
6. ((time factors[MeSH Terms]) AND ((((erythrocyte transfusion[MeSH Terms]) OR erythrocytes[MeSH Terms]) OR blood component transfusion[MeSH Terms]) OR blood transfusion[MeSH Terms])) AND ((((Intensive Care Units[MeSH Terms]) OR Intensive Care[MeSH Terms]) OR Critical Illness[MeSH Terms]) OR Critical Care[MeSH Terms])
7. #5 OR #6
8. #7 Filters: Clinical Trial; Humans

OVID=794

1. (erythrocyte* or red cell* or red blood cell* or RBC* or blood).mp. [mp=title, abstract, full text, caption text]
2. (retransfus* or transfuse* or infuse*).mp. [mp=title, abstract, full text, caption text]
3. (Blood Preservation or age* or aging or fresh* or old* or new* or young* or store* or storage or storing or preserv*).mp. [mp=title, abstract, full text, caption text]
4. (Critical Illness or Critical Care or Intensive Care or Intensive Care Units or

Critically ill or Critical* or Intensive*).mp. [mp=title, abstract, full text, caption text]

5. #1 AND #2 AND #3 AND #4
6. #5 AND "Article" [Publication Type] AND yr="1860-2017".

Web of Science=2717

TS=(erythrocyte* or red cell* or red blood cell* or RBC* or blood) AND TS=(retransfus* or transfuse* or infuse*) AND TS=(Blood Preservation or age* or aging or fresh* or old* or new* or young* or store* or storage or storing or preserv*) AND TS=(Critical Illness or Critical Care or Intensive Care or Intensive Care Units or Critically ill or Critical* or Intensive*)

Cochrane Library=30

1. MeSH descriptor: [Erythrocyte Transfusion] explode all trees
2. MeSH descriptor: [Erythrocytes] explode all trees
3. MeSH descriptor: [Blood Component Transfusion] explode all trees
4. MeSH descriptor: [Blood Transfusion] explode all trees
5. #1 or #2 or #3 or #4
6. MeSH descriptor: [Time Factors] explode all trees
7. MeSH descriptor: [Intensive Care Units] explode all trees
8. MeSH descriptor: [Critical Care] explode all trees
9. MeSH descriptor: [Critical Illness] explode all trees
10. #7 or #8 or #9
11. #5 and #6 and #10

Appendix 2. The reasons for exclusion of the 23 ineligible studies are listed as follow:

Trials	Reasons for exclusion
Lacroix/2015[s1]	Duplicate publication (1 trial)
Walsh/2004[s2]; Damiani/2015[s3]	without any endpoints (2 trials)
Yamal/2015[s4]; Cywinski/2013[s5]	Non-randomized trials (2 trials)
Leal-Noval/2003[s6]	Prospective cohort study (1 trial)
Cartotto/2014[s7]	Retrospective study (1 trial)
Leal-Noval/2008[s8]; Kaukonen/2013[s9]; Pettilä/2011[s10]	Observational studies (3 trial)
Hebert/2005[s11]	The subjects in this study, which enrolled 42 patients undergoing cardiovascular surgery and 15 critically ill patients, are not exactly critically ill patients.
Heddle/2012[s12]	Although this trial was conducted in acute care hospital, the subjects was enrolled from emergency department, clinic or other department, but not from ICU.
Weiskopf/2006[s13]; van de Watering/2006[s14]; Bennett-Guerrero/2009[s15]; Hod/2011[s16]; Roberson/2012[s17]; Berra/2014[s18]; Neuman/2015[19]; Steiner/2015[s20]; Risbano/2015[s21]; Bao/2017[s22]; Spadaro/2017[s23]	The subjects are not critically ill patients admitted to ICU (11 trials)

SUPPLEMENTARY REFERENCE

s1. Lacroix J, Hébert PC2, Fergusson D3, Tinmouth A4, Capellier G5, Tiberghien P, et al. The ABLE study: A randomized controlled trial on the efficacy of fresh red cell units to improve the outcome of transfused critically ill adults. Transfus Clin Biol. 2015;22(3):107-11. [Article in French].

s2. Walsh TS, McArdle F, McLellan SA, Maciver C, Maginnis M, Prescott RJ, et al. Does the storage time of transfused red blood cells influence regional or global indexes of tissue oxygenation in anemic critically ill patients? Crit Care Med.2004;32(2):364–371.

s3. Damiani E, Adrario E, Luchetti MM, Scorcella C, Carsetti A, Mininno N, et al. Plasma free hemoglobin and microcirculatory response to fresh or old blood transfusions in sepsis. PLoS One. 2015; 10(5):e0122655.

s4. Yamal JM, Benoit JS, Doshi P, Rubin ML, Tilley BC, Hannay HJ, et al. Association of transfusion red blood cell storage age and blood oxygenation, long-term neurologic outcome, and mortality in traumatic brain injury. J Trauma Acute Care Surg. 2015;79(5):843-9.

s5. Cywinski JB, You J, Argalious M, Irefin S, Parker BM, Fung JJ, et al. Transfusion of Older Red Blood Cells Is Associated With Decreased Graft Survival After Orthotopic Liver Transplantation. Liver Transpl. 2013;19(11):1181-8.

s6. Leal-Noval SR, Jara-López I, García-Garmendia JL, Marín-Niebla A, Herruzo-Avilés A, Camacho-Laraña P, et al. Influence of erythrocyte concentrate storage time on postsurgical morbidity in cardiac surgery patients. Anesthesiology. 2003;98(4):815-22.

s7. Cartotto R, Yeo C, Camacho F, Callum J. Does the storage age of transfused blood affect outcome in burn patients? J Burn Care Res. 2014;35(2):186-97.

s8. Leal-Noval SR, Muñoz-Gómez M, Arellano-Orden V, Marín-Caballos A, Amaya-Villar R, Marín A, et al. Impact of age of transfused blood on cerebral oxygenation in male patients with severe traumatic brain injury.

Crit Care Med. 2008;36(4):1290-6.

s9. Kaukonen KM, Vaara ST, Pettilä V, Bellomo R, Tuimala J, Cooper DJ, et al. Age of red blood cells and outcome in acute kidney injury. Crit Care. 2013; 17(5):R222.

s10. Pettilä V, Westbrook AJ, Nichol AD, Bailey MJ, Wood EM, Syres G, et al. Age of red blood cells and mortality in the critically. Crit Care. 2011;15(2):R116.

s11. Hébert PC, Chin-Yee I, Fergusson D, Blajchman M, Martineau R, Clinch J, et al. A pilot trial evaluating the clinical effects of prolonged storage of red cells. Anesth Analg. 2005;100(5):1433-8, table of contents.

s12. Heddle NM, Cook RJ, Arnold DM, Crowther MA, Warkentin TE, Webert KE, et al. The effect of blood storage duration on in-hospital mortality: a randomized controlled pilot feasibility trial. Transfusion. 2012;52(6):1203-1212.

s13. Weiskopf RB, Feiner J, Hopf H, Lieberman J, Finlay HE, Quah C, et al. Fresh blood and aged stored blood are equally efficacious in immediately reversing anemia-induced brain oxygenation deficits in humans. Anesthesiology. 2006;104(5):911-20.

s14. 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):1712-8.

s15. Bennett-Guerrero E, Stafford-Smith M, Waweru PM, Bredehoeft SJ, Campbell ML, Haley NR, et al. A prospective, double-blind, randomized clinical feasibility trial of controlling the storage age of red blood cells for transfusion in cardiac surgical patients. Transfusion. 2009;49(7):1375-83.

s16. Hod EA, Brittenham GM, Billote GB, Francis RO, Ginzburg YZ, Hendrickson JE, et al. Transfusion of human volunteers with older, stored red blood cells produces extravascular hemolysis and circulating non-transferrin-bound iron. Blood. 2011;118(25):6675-82.

s17. Roberson RS, Lockhart E, Shapiro NI, Bandarenko N, McMahon TJ, Massey MJ, et al. Impact of transfusion of autologous 7- versus 42-day-old AS-3 red blood cells on tissue oxygenation and the microcirculation in healthy volunteers. Transfusion. 2012;52(11):2459-64.

s18. Berra L, Pinciroli R, Stowell CP, Wang L, Yu B, Fernandez BO, et al.

Autologous transfusion of stored red blood cells increases pulmonary artery pressure. Am J Respir Crit Care Med. 2014;190(7):800-7.

s19. Neuman R, Hayek S, Rahman A, Poole JC, Menon V, Sher S, et al. Effects of storage-aged red blood cell transfusions on endothelial function in hospitalized patients. Transfusion. 2015;55(4):782-90.

s20. Steiner ME, Ness PM, Assmann SF, Triulzi DJ, Sloan SR, Delaney M, et al. Effects of red-cell storage duration on patients undergoing cardiac surgery. N Engl J Med. 2015;372(15):1419-29.

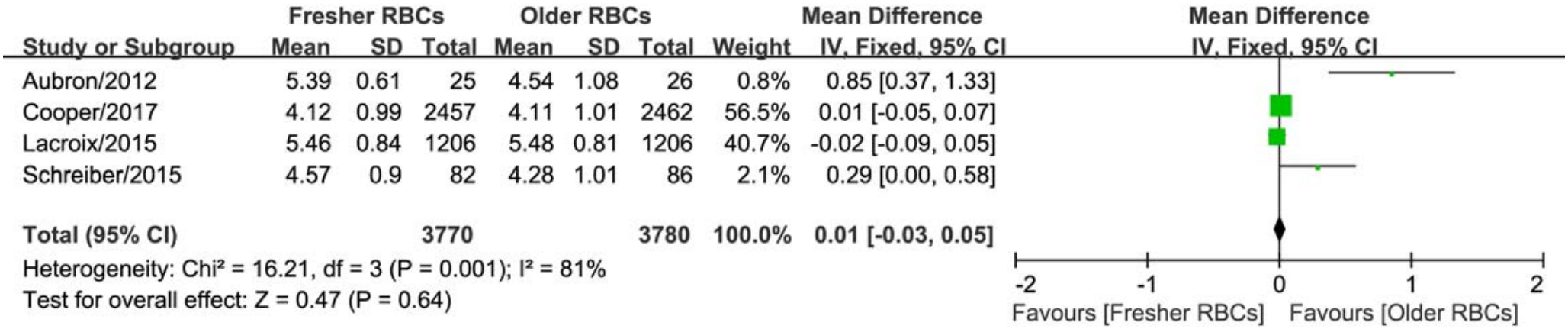
s21. Risbano MG, Kanias T, Triulzi D, Donadee C, Barge S, Badlam J, et al. Effects of Aged Stored Autologous Red Blood Cells on Human Endothelial Function. Am J Respir Crit Care Med. 2015;192(10):1223-33.

s22. Bao HX, Tong PJ, Li CX, Du J, Chen BY, Huang ZH, et al. Efficacy of fresh packed red blood transfusion in organophosphate poisoning. Medicine (Baltimore). 2017;96(11):e6375.

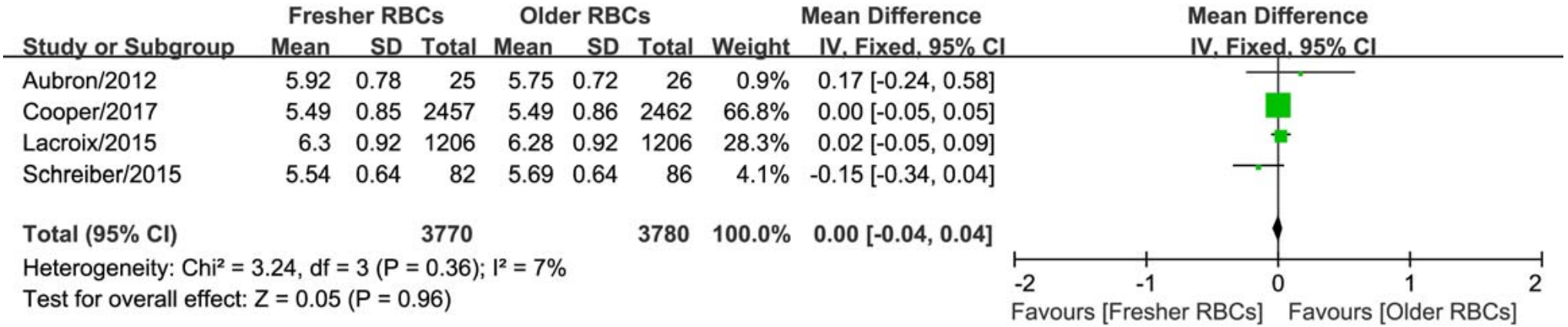
s23. Spadaro S, Taccone FS, Fogagnolo A, Fontana V, Ragazzi R, Verri M, et al. The effects of storage of red blood cells on the development of postoperative infections after noncardiac surgery. Transfusion. 2017;57(11):2727-2737.

SUPPLEMENTARY MATERIAL

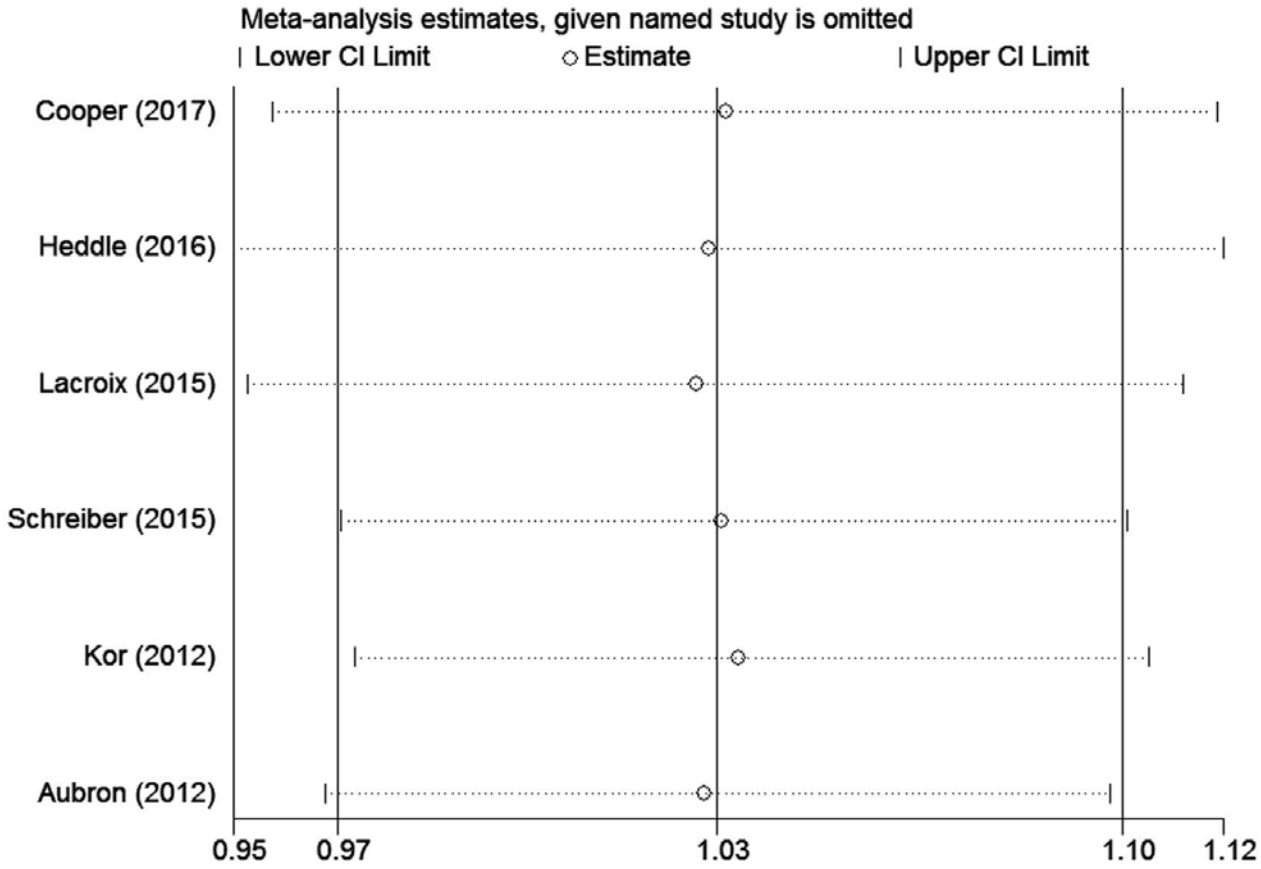
Supplementary Figure 1. Forest plot of meta-analysis for the duration of intensive care unit stay. Mean and SD on the log scale and the unit is log hours. RBC red blood cell; SD standard deviation; IV inverse variance.



Supplementary Figure 2. Forest plot of meta-analysis for the duration of hospital stay. Mean and SD on the log scale and the unit is log hours.RBC red blood cell; SD standard deviation; IV inverse variance.



Supplementary Figure 3. Sensitivity analysis for assessing the robustness of pooled OR for short-term mortality. The overall effect of storage age of transfused RBCs on short-term mortality was unchanged after sequentially removing one study at a time.



Sepplementary table 1. The conventional meta-analysis and TSA using random-effects and fixed-effects for all endpoints.

	Conventional meta-analysis						TSA, with α of 5%, power of 80%, relative risk reduction of 15%, two-tailed					
	Random-effects			Fixed-effects			Random-effects			Fixed-effects		
	OR(95%CI)	*P*	I^2	OR(95%CI)	*P*	I^2	TSA-adjusted 95%CI	Incidence in control arm	diversity (D^2)	TSA-adjusted 95%CI	Incidence in control arm	diversity (D^2)
Primary endpoint												
All trials	1.04(0.96 -1.13)	0 .312	%	1.04(0.96 -1.13)	0.3 09	%	0.90-1.21	16.4%	0%	0.90-1.21	16.4%	0%
Multi-center trials	1.04(0.96 -1.13)	0 .292	%	1.04(0.96 -1.13)	0.2 92	%						
Single-center trials	1.16(0.28 -4.71)	0 .839	6.7 %	0.91(0.44 -1.85)	0.7 89	6.7 %						
Trials with Low risk of bias	1.04(0.94 -1.16)	0 .445	%	1.04(0.94 -1.16)	0.4 40	%	0.89-1.22	22.9%	0%	0.89-1.22	22.9%	0%
Secondary endpoints	Mean difference (95%CI) on the log scale											
Duration of ICU stay	0.10(-0.0 4 to 0.24)	0 .163	1.5 %	0.01(-0.0 3 to 0.05)	0.6 38	1.5 %						
Duration of hospital stay	0.00(-0.0 4 to 0.04)	0 .978	.4 %	0.00(-0.0 4 to 0.04)	0.9 57	.4 %						

The older RBCs group was taken as a reference. ICU intensive care unit; OR odds ratio; CI confidence interval; TSA trial sequential analysis