Relation of Use of Red Blood Cell Transfusion After Acute Coronary Syndrome to Long-Term Mortality

Jaakko Allonen, MD[a,*], Markku S. Nieminen, MD, PhD[a], Seppo Hiippala, MD, PhD[b], and Juha Sinisalo, MD, PhD[a]

Registry studies have associated red blood cell (RBC) transfusion with increased in-hospital mortality in patients with acute coronary syndrome (ACS). The impact on long-term mortality after 1-year follow-up remains unknown. Consecutive patients with ACS (n = 2,009) of a prospective Genetic Predisposition of Coronary Artery Disease cohort were followed for a median of 8.6 years (95% confidence interval [CI] 8.59 to 8.69). After discharge, 1,937 (96%) patients survived for over 30 days. Of those survivors, a subgroup of previously transfusion-naïve patients 85/1,937 (4.4%) who had received at least 1 RBC transfusion during hospitalization were compared with 1,278/1,937 patients (66.0%) who had not received any transfusion either during the hospitalization or the entire follow-up. Unadjusted long-term mortality was significantly higher in the patients transfused with RBC compared with their counterparts not transfused with RBC (58.8% vs 20.3%, p <0.001). The results remained significant for hazard ratio (HR) 1.91, 95% CI 1.39 to 2.63, p <0.001, after multivariate Cox proportional hazards model analysis and were similar after 1-year landmark analysis (HR 1.90, 95% CI 1.34 to 2.70, p <0.001). The higher all-cause mortality was largely explained by cancer mortality (15.3% vs 4.1%, p <0.001) and cardiovascular mortality (34.1% vs 12.1%, p <0.001). After 1:1 propensity score matching (n = 65 vs 65), the association of RBC transfusion with worse survival remained significant (HR 2.70, 95% CI 1.48 to 4.95, p = 0.001). Inverse probability weighted Cox analyses turned out similar results (HR 2.07, 95% CI 1.38 to 3.11, p <0.001). In conclusion, the strong association of need for RBC transfusion with increased mortality continued for patients with ACS even after a 1-year follow-up. **(Am J Cardiol 2018;121:1496–1504)**

Evolving percutaneous coronary intervention techniques and antithrombotic medications are enabling the treatment of more fragile patients with co-morbid acute coronary syndrome (ACS) who are at risk of different complications, including bleeding increase.[1] Patients with ACS who are anemic and bleeding are treated by red blood cell (RBC) transfusion to maintain sufficient hemoglobin (Hb) levels and oxygenation, and to minimize the ischemia of the myocardium.[2] Guidelines suggest using a more restrictive transfusion strategy for symptomless patients with stable coronary artery disease to maintain an Hb level >80 g/L instead of a liberal transfusion strategy (with a threshold Hb of 100 g/L).[3–5] However, there is little consensus at present about the use of transfusions for patients with ACS, albeit some registry studies demonstrate the need for a more restrictive strategy on patients with ACS.[6,7] Randomized controlled trials on patients with ACS have concluded controversial results both for and against the benefits of the liberal transfusion strategy,[8,9] whereas it was linked to better or at least equal survival on critically ill patients in intensive care in the noncardiology field.[10,11] A recent meta-analysis conducted by Docherty et al suggests still using more liberal transfusion strategy to all cardiac patients until adequately powered randomized trials have confirmed the best practice.[12] Registry studies have associated RBC transfusion as an independent contributor with increased mortality in patients with ACS up to a 1-year mortality.[7,13–16] The impact of RBC transfusion on long-term mortality (i.e., after 1 year), however, remains unknown. The objective of our study was to determine how RBC transfusion affects morbidity and mortality in patients with ACS in the long term. Moreover, we examined the possible reasons for increased mortality by analyzing patients' causes of death.

Methods

A prospective Genetic Predisposition of Coronary Artery Disease cohort consists of 5,809 consecutive patients assigned for coronary angiography between March 2006 and March 2008 in the Helsinki University Central Hospital.[17] The study register contains comprehensive information gathered from patient records and a 2-page patient questionnaire. The register incorporates medical history, current condition, cardiovascular risk factors, medications, electrocardiogram, echocardiography, and coronary angiography results. This study comprises 2,090 patients with ACS in the Genetic Predisposition of Coronary Artery Disease cohort.[18] The follow-up lasted until December 31, 2015, or until the patient's death, whichever occurred first. The median follow-up was 8.6 years,

[a]Heart and Lung Center, Helsinki University Hospital and Helsinki University, Helsinki, Finland; and [b]Anaesthesiology and Critical Care, Helsinki University Hospital and Helsinki University, Helsinki, Finland. Manuscript received November 1, 2017; revised manuscript received and accepted February 26, 2018.

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*Corresponding author: Tel: +35840 532 8606; fax: +358 9 47174574.
E-mail address: jaakko.allonen@helsinki.fi (J. Allonen).

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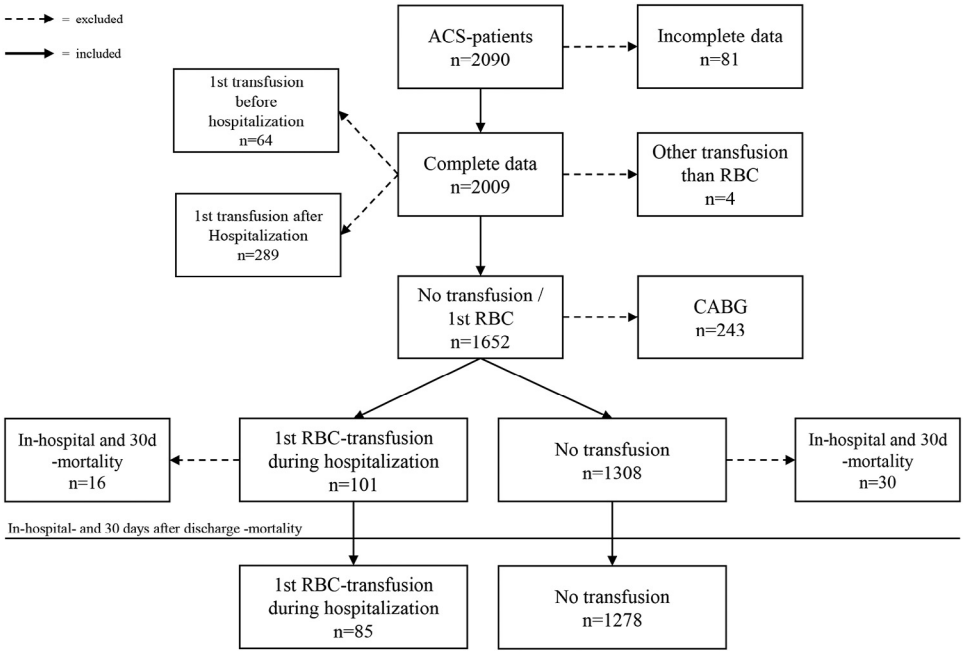

Figure 1. Patient selection.

and it was assessed by Schemper's method (95% confidence interval [CI] 8.59 to 8.69). We gathered data about transfusions and Hb levels from a comprehensive hospital transfusion registry of The Hospital District of Helsinki and Uusimaa to determine the impact of blood transfusion on the survival of patients with ACS. These data and other additional data sets used are presented in detail in Appendix S1.[19–21] The primary outcomes measured were all-cause mortality, overall survival (OS), and survival after a 1-year landmark (1YLS).

We had complete data for 2,009/2,090 patients with ACS (96%) by the end of the analyses. After the exclusion and inclusion criteria (Figure 1 and Appendix S1) were applied, a group of 85 previously RBC-transfusion-naïve patients who did not undergo coronary artery bypass grafting (CABG) but received at least 1 RBC transfusion during hospitalization were compared with the 1,278 patients who had not received any transfusion either during the hospitalization or the entire follow-up (nontransfusion group). The primary outcomes measured were all-cause mortality and OS. The secondary outcomes were cancer incidence and cancer mortality. Because of wide heterogeneity in both the size and demographics of the compared groups, we conducted a 1:1 propensity score matching to even up the differences and thoroughly adjust for confounding. All the baseline variables with significant difference on the level 0.05 were included in the logistic regression model to adjust for the propensity of being treated with RBC transfusion. Matching yielded 65 patients in each group to be compared. In the matched sample the propensity score was then included in the final confounder-adjusted multivariable model. All patients gave their signed informed consent. The Ethics Committee of the Hospital District of Helsinki and Uusimaa, Helsinki, Finland, approved the research protocol, and this study complies with the Declaration of Helsinki 1964 and revisions thereafter.

Data are given as percentages, mean ± SD, or median with interquartile range (25 to 75 percentiles). Categorical variables between different groups were analyzed with cross-tabulation using a chi-squared test or Fisher's exact test, whichever was applicable. Continuous scale variables were analyzed by either the independent *t* test or the nonparametric Mann–Whitney *U* test, whichever was appropriate. The normality of distribution within continuous scale variables was assessed graphically and with the Kolmogorov–Smirnov test. Various factors that contribute to the long-term survival of patients were adjusted using multivariate Cox proportional hazards models both before and after the propensity score matching. The effect of each variable on survival was assessed with both Kaplan–Meier and the univariable Cox regression model. All candidate variables with significance on the level 0.05 in univariable analyses were introduced to multivariate models with both stepwise and backward variable-reduction techniques to form the final equations. Candidate confounding factors are described in the supplementary material (Appendix S1). The assumption of proportional hazards was tested both graphically and by plotting Shoenfeld's residuals against the survival time. No violations of proportionality were observed. Interactions between each variable were tested within a 2-variable Cox regression model with their interaction term included, and warfarin as a discharge medication was excluded from the multivariate analyses because it had a marked interaction with atrial fibrillation. Multicollinearity was assessed by analyzing the variance inflation factors between independent variables. A variance inflation factor value over 2.50 was considered as a threshold of significant multicollinearity, and no violation was encountered. Hazard ratios (HRs) with their 95% CI and survival curves are reported. To inflate the small cohort size (especially in terms of RBC-treated patients) and to verify our results even after propensity matching, we conducted an

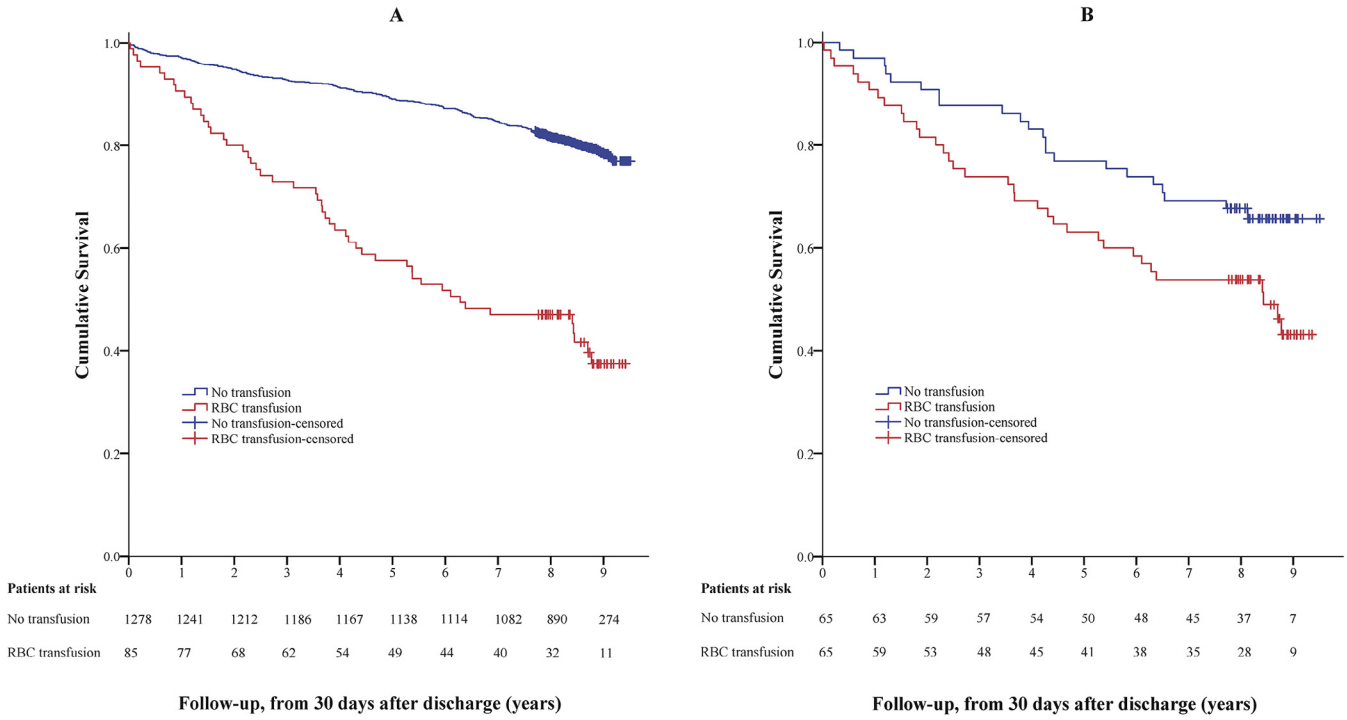

Figure 2. (*A*) Univariate analysis (Kaplan–Meier) of OS between RBC-transfused and non–RBC-transfused patients within an unmatched cohort. (*B*) Univariate analysis (Kaplan–Meier) of OS between RBC-transfused and non–RBC-transfused patients after propensity score matching (color reproduction only on the Web).

inverse probability of treatment weighted (IPTW) Cox regression model both for OS and survival after a 1YLS. All tests were 2 sided and used significance levels below the probability of 0.05 to assume statistical significance. Statistical analyses were run on IBM SPSS Statistics 24.0 software (SPSS, Inc., Chicago, Illinois).

Results

The RBC-transfused patients who did not undergo CABG and survived for over 30 days after discharge (n = 85) received a median of 5 (interquartile range 2 to 9) transfusions and 8 (interquartile range 4 to 17.5) units of packed RBCs cumulatively per patient. These previously transfusion-naïve patients received their first RBC transfusion at a mean of 5.6 days (±6.3) after admission and 4.2 days (±6.2) after angiography. Causes of bleeding and indications for transfusion within RBC-transfused patients are listed in Table 1. The overall mortality of RBC-transfused patients was almost threefold that of patients without RBC transfusion (58.8% [50/85] vs 20.3% [259/1,278], p <0.001) in the follow-up period from 30 days after discharge until the end of the follow-up. Estimated mean survivals were 5.9 years (95% CI 5.2 to 6.7) versus 8.5 years (95% CI 8.4 to 8.6), p <0.001 (Figure 2A). Patients treated with RBC transfusion were generally older; had more diseases such as diabetes, hypertension, kidney disease, previous cancer, and atrial fibrillation; had a more severe coronary artery disease (3-artery disease); and were more often both female and anemic (Table 2). After propensity score matching, the overall mortality of RBC-transfused patients remained significantly higher than non–RBC-transfused patients. Excluding Hb values, there were no significant differences between RBC-transfused and non–RBC-transfused patients after the matching (Table 2). Mean survival differed markedly as well between the matched groups (6.3 years [95% CI 5.5 to 7.1] vs 7.6 years [95% CI 6.9 to 8.3], p = 0.035, respectively; Figure 2B). Propensity matching was adequately conducted with good statistical discrimination (C-statistic 0.91, 95% CI 0.88 to 0.94).

Table 1
Bleeding causes and indications for red blood cell-transfusion. (n = 85)

Cause of bleeding / Primary indication for transfusion	
Low hemoglobin (no mention of bleeding in patient records)	36 (42%)
Access site bleeding (femoral)	26 (31%)
Gastrointestinal bleeding	7 (8%)
Retroperitoneal hematoma	2 (2%)
Peritoneal bleeding	1 (1%)
Perioperative transfusion (related to i.e. vascular procedure)	5 (6%)
Chronic anemia	4 (5%)
Cancer related	1 (1%)
Hematuria	2 (2%)
Procedure complication (Coronary rupture)	1 (1%)
Total	**85 (100%)**
Secondary indication for transfusion	
Gastrointestinal bleeding	1 (1%)
Retroperitoneal hematoma	1 (1%)
Peritoneal bleeding	1 (1%)
Perioperative transfusion (related to aortic dissection and cardiac tamponade)	2 (2%)
Acute kidney failure	1 (1%)
Intracranial hemorrhage	1 (1%)
Total	**7** (8%)

Table 2
Patient characteristics

	Non-matched cohort				Propensity score matched cohort			
	Valid cases	No transfusion (n = 1278)	RBC transfusion (n = 85)	p	Valid cases	No transfusion (n = 65)	RBC transfusion (n = 65)	p
Demographics								
Age (years, mean, standard deviation)	1363	63.6 (±12.0)	71.1 (±10.8)	<0.001 *	130	68.8 (±12.4)	69.7 (±11.1)	0.650 *
Age > 65 years	1363	586 (46%)	59 (69%)	<0.001	130	40 (62%)	42 (65%)	0.716
Age > 80 years	1363	121(10%)	21 (25%)	0.004	130	12 (19%)	15 (23%)	0.517
Women	1363	349 (27%)	46 (54%)	<0.001 *	130	37 (57%)	35 (54%)	0.724
Body mass index (kg/m^2, mean, standard deviation)	1350	27.6 (±4.9)	26.6 (±4.4)	0.060 *	129	27.8 (±6.0)	26.6 (±4.4)	0.278 *
Smoker/ex-smoker	1351	830 (66%)	50 (60%)	0.334	127	33 (52%)	37 (59%)	0.417
Co-morbidities								
Diabetes mellitus	1363	248 (19%)	25 (29%)	0.026 *	130	21 (32%)	16 (25%)	0.331 *
Hypertension	1363	797 (62%)	63 (74%)	0.030 *	130	51 (79%)	48 (74%)	0.537
Kidney disease	1363	14 (1%)	8 (9%)	<0.001 *	130	4 (6%)	4 (6%)	1.000 *
Peripheral artery disease	1349	75 (6%)	16 (19%)	<0.001 *	130	10 (15%)	10 (15%)	1.000
Atrial fibrillation	1363	84 (7%)	14 (7%)	0.001 *	130	5 (8%)	9 (14%)	0.258 *
Cerebrovascular disease	1352	120 (10%)	12 (14%)	0.171 *	130	5 (8%)	8 (12%)	0.380 *
Prior myocardial infarction	1349	233 (18%)	17 (20%)	0.678 *	130	16 (25%)	14 (22%)	0.677 *
Baseline anemia	1295	281 (23%)	63 (74%)	<0.001 *	130	49 (75%)	45 (69%)	0.433
Anemia at discharge	876	343 (42%)	55 (86%)	<0.001	95	36 (75%)	41 (87%)	0.128
Prior procedures								
Coronary artery bypass grafting	1363	119 (9%)	6 (7%)	0.486 *	130	8 (12%)	5 (8%)	0.380 *
Percutaneous coronary intervention	1363	141 (11%)	11 (13%)	0.540 *	130	7 (11%)	9 (14%)	0.593 *
Vascular operation: lower limb	1360	26 (2%)	5 (6%)	0.040 *	130	0 (0%)	2 (3%)	0.154 *
Characteristics of coronary disease								
Number of coronary arteries narrowed								
1 artery	1363	718 (56%)	26 (31%)	<0.001 *	130	29 (45%)	20 (31%)	0.103 *
2 arteries	1363	332 (26%)	30 (35%)	0.060 *	130	17 (26%)	25 (39%)	0.134
3 arteries	1363	163 (13%)	26 (31%)	<0.001 *	130	16 (25%)	17 (26%)	0.840 *
Left main disease	1363	40 (3%)	5 (6%)	0.196 *	130	1 (2%)	4 (6%)	0.171
Culprit lesion								
Left main	1363	1 (0.1%)	0 (0%)	0.796	130	0 (0%)	0 (0%)	-
Left anterior descending	1363	79 (6%)	5 (6%)	0.912	130	2 (3%)	5 (8%)	0.244
Left circumflex	1363	29 (2%)	3 (4%)	0.457	130	1 (2%)	2 (3%)	0.559
Right	1363	75 (6%)	5 (6%)	0.996	130	5 (8%)	5 (8%)	1.000
No culprit / Not available	1363	1094 (86%)	72 (85%)	0.820	130	57 (88%)	53 (82%)	0.331
Acute coronary syndrome-type								
Unstable angina pectoris	1363	135 (11%)	8 (9%)	0.737	130	4 (6%)	6 (9%)	0.510
Non-ST-elevation myocardial infarction	1363	639 (50%)	39 (46%)	0.462 *	130	33 (51%)	26 (40%)	0.218
ST-elevation myocardial infarction	1363	504 (39%)	38 (45%)	0.336 *	130	28 (43%)	33 (51%)	0.380 *
Cardiopulmonary resuscitation	1363	22 (2%)	11 (13%)	<0.001	130	5 (8%)	7 (11%)	0.545
Left ventricular ejection fraction								
< 20%	664	3 (0.5%)	2 (3%)	0.067	80	0 (0%)	2 (5%)	0.195
20–35%	664	49 (8%)	2 (3%)	0.304	80	4 (11%)	1 (2%)	0.104
35–50%	664	191 (32%)	27 (45%)	0.035	80	12 (33%)	23 (52%)	0.089
>50%	664	361 (60%)	29 (48%)	0.086	80	20 (56%)	18 (41%)	0.192
Procedures								
Percutaneous coronary intervention	1363	1067 (84%)	71 (84%)	0.992 *	130	54 (83%)	56 (86%)	0.627
Bare-metal stent	1149	845 (78%)	48 (68%)	0.507	110	41 (76%)	38 (68%)	0.552
Drug-eluting stent	1149	154 (14%)	11 (16%)	0.507	110	7 (13%)	9 (16%)	0.552
Without stenting	1149	79 (7%)	12 (17%)	0.012	110	6 (11%)	9 (16%)	0.629
Radial access	1343	27 (2%)	2 (2%)	0.545 *	128	3 (5%)	1 (2%)	0.325
Thrombolysis	1363	184 (14%)	10 (12%)	0.501 *	130	7 (11%)	10 (15%)	0.435
Kidney function								
Glomerular filtration rate (ml/min/1.73 m^2, mean, standard deviation)	1313	84.6 (±19.1)	66.8 (±27.7)	<0.001	130	76.9 (±21.5)	71.1 (±26.2)	0.170
Glomerular filtration rate <60 ml/min/1.73 m^2	1313	144 (12%)	33 (39%)	<0.001 *	130	17 (26%)	21 (32%)	0.441 *

(*continued*)

Table 2
(*continued*)

	Non-matched cohort				Propensity score matched cohort			
	Valid cases	No transfusion (n = 1278)	RBC transfusion (n = 85)	p	Valid cases	No transfusion (n = 65)	RBC transfusion (n = 65)	p
Hemoglobin								
Admission (g/l, mean, standard deviation)	1295	135.7 (±14.3)	111.3 (±21.1)	<0.001	130	121.0 (±15.2)	112.6 (±22.5)	0.008
Highest (during hospitalization) (g/l, mean, standard deviation)	1250	139.0 (±14.1)	122.1 (±6.3)	<0.001	127	126.4 (±15.9)	123.3 (±17.2)	0.167
Angiography (g/l, mean, standard deviation)	1299	134.7 (±14.3)	108.7 (±20.9)	<0.001	129	120.1 (±13.6)	109.4 (±21.7)	0.001
Nadir (during hospitalization) (g/l, mean, standard deviation)	1252	127.3 (±15.0)	85.1 (±9.7)	<0.001	127	111.3 (±14.6)	85.7 (±10.0)	<0.001
Discharge (g/l, mean, standard deviation)	876	129.0 (±15.2)	106.3 (±14.4)	<0.001	122	116.7 (±15.0)	105.6 (±14.9)	0.001
1–3 months (g/l, mean, standard deviation)	615	139.5 (±13.9)	126.0 (±13.9)	<0.001	80	127.9 (±13.0)	126.3 (±14.0)	0.597
6–18 months (g/l, mean, standard deviation)	816	144.5 (±13.1)	130.5 (±15.7)	<0.001	91	137.4 (±14.0)	131.1 (±16.6)	0.053
1–4 years (g/l, mean, standard deviation)	972	148.6 (±12.4)	134.7 (±13.9)	<0.001	97	143.7 (±13.0)	134.9 (±14.1)	0.002
Hematocrit (during hospitalization) (g/l, mean, standard deviation)	1329	41.1 (±4.0)	35.1 (±5.4)	<0.001	130	38.3 (±4.8)	35.3 (±5.8)	0.001
Mortality								
Overall-mortality	1363	259 (20%)	50 (59%)	<0.001	130	22 (34%)	34 (52%)	0.034
Cardiovascular	1363	154 (12%)	29 (34%)	<0.001	130	14 (22%)	22 (34%)	0.117
Myocardial infarction	1363	122 (10%)	23 (27%)	<0.001	130	10 (15%)	17 (26%)	0.130
Cancer	1363	52 (4%)	13 (15%)	<0.001	130	4 (6%)	7 (11%)	0.344
Blood related / Lymphomas	1363	2 (0.2%)	1 (1%)	0.176	130	0 (0%)	1 (2%)	1.000
Urinary tract	1363	3 (0.2%)	2 (2%)	0.034	130	0 (0%)	0 (0%)	-
Prostate	1363	4 (0.3%)	1 (1%)	0.276	130	0 (0%)	0 (0%)	-
Breast	1363	3 (0.2%)	2 (2%)	0.034	130	1 (2%)	2 (3%)	1.000
Mesothelioma / Other soft tissue	1363	2 (0.2%)	1 (1%)	0.176	130	0 (0%)	0 (0%)	-
Melanoma	1363	1 (0.1%)	0 (0%)	1.000	130	0 (0%)	0 (0%)	-
Respiratory system /thoracic cavity	1363	18 (1%)	2 (2%)	0.358	130	1 (2%)	2 (3%)	1.000
Gastrointestinal system	1363	17 (1%)	4 (5%)	0.037	130	2 (3%)	2 (3%)	1.000
Unspecified / Metastasis	1363	2 (0.2%)	0 (0%)	1.000	130	0 (0%)	0 (0%)	-
Discharge medications								
Clopidogrel	1363	1189 (93%)	64 (75%)	<0.001 *	130	52 (80%)	53 (82%)	0.824 *
Warfarin	1320	44 (4 %)	7 (8%)	0.041 *	130	4 (6%)	6 (9%)	0.510
Angiotensin Converting Enzyme– inhibitor	1359	750 (59%)	47 (55%)	0.517	130	35 (54%)	38 (59%)	0.596
Angiotensin Receptor blocker	1361	188 (15%)	17 (20%)	0.189	130	10 (15%)	14 (22%)	0.366
Beta—blocker	1362	1164 (91%)	78 (92%)	0.847	130	59 (91%)	60 (92%)	0.753
Calcium channel blocker	1358	144 (11%)	19 (22%)	0.002 *	130	11 (17%)	13 (20%)	0.651 *
Digoxin	1356	15 (1%)	3 (4%)	0.095 *	130	0 (0%)	2 (3%)	0.154
Diuretic	1360	244 (19%)	42 (49%)	<0.001 *	130	26 (40%)	28 (43%)	0.722 *
Insulin	1355	85 (7%)	16 (19%)	<0.001 *	130	10 (15%)	10 (15%)	1.000 *
Pain killer	1350	39 (3%)	11 (13%)	<0.001 *	130	7 (11%)	6 (9%)	0.770
Statin	1363	1234 (97%)	81 (95%)	0.536 *	130	61 (94%)	64 (99%)	0.171
Nitrate	1360	214 (17%)	22 (26%)	0.032 *	130	13 (20%)	15 (23%)	0.670 *
Acetylsalicylic acid	1363	1203 (94%)	81 (95%)	0.813 *	130	59 (91%)	63 (97%)	0.144
Malignancies during follow-up								
Bone marrow related, lymphomas	1363	9 (0.7 %)	2 (2%)	0.147	130	0 (0%)	2 (3%)	0.496
Unspecified / Metastasis	1363	4 (0.3%)	0 (0%)	1.000	130	1 (2%)	0 (0%)	1.00
Central nervous system and eye related	1363	2 (0.2%)	0 (0%)	1.000	130	0 (0%)	0 (0%)	-
Urinary tract	1363	12 (0.9%)	2 (2%)	0.216	130	0 (0%)	0 (0%)	-
Prostate	1363	35 (3%)	4 (5%)	0.300	130	3 (5%)	3 (5%)	1.000
Uterus and ovaries	1363	1 (0.1%)	0 (0%)	1.000	130	0 (0%)	0 (0%)	-
Breast	1363	17 (1%)	3 (4%)	0.124	130	2 (3%)	3 (5%)	1.000
Mesothelioma / other soft tissues	1363	1 (0.1%)	1 (1%)	0.121	130	1 (2%)	0 (0%)	1.000
Melanoma / other skin malignancies	1363	48 (4%)	0 (0%)	0.069	130	3 (5%)	(0%)	0.244
Respiratory system / thoracic cavity	1363	25 (2%)	2 (2%)	0.683	130	1 (2%)	2 (3%)	1.000
Gastrointestinal system	1363	19 (2%)	4 (5%)	0.050	130	1 (2%)	2 (3%)	1.000
Oro-pharyngeal cavity and lip	1363	8 (0.6%)	1 (1%)	0.441	130	0 (0%)	1 (2%)	1.000
Malignancies in total	1363	181 (14%)	19 (22%)	0.039	130	12 (19%)	13 (20%)	0.824

RBC = Red blood cell.
* < 0.05 significance on survival in an univariable Cox regression.

Covariate balance after propensity matching was also assessed with the Hosmer–Lemeshow goodness-of-fit test, chi-square 3.64, p = 0.888, which indicated that good balance was achieved.

Adjusted multivariate analysis revealed that RBC transfusion was a significant independent factor for OS in an unmatched cohort (HR 1.91, 95% CI 1.39 to 2.63, p <0.001) (Table 3). In a 1YLS multivariate Cox proportional hazards model, RBC transfusion remained a strong contributing factor of survival with an almost twofold relative risk of mortality (Table 3). These findings were affirmed after the propensity score matching. In final adjusted models within the matched cohort, the RBC transfusion more than doubled the relative risk of mortality both on OS and on 1YLS (Table 3). In addition, an adjusted IPTW Cox proportional hazards model verified that RBC transfusion was associated with worse prognoses in both OS (weighted n = 2,130.6) and 1YLS (weighted n = 2,012.0) (HR 1.70, 95% CI 1.11 to 2.59, p = 0.015 and HR 2.07, 95% CI 1.38 to 3.11, p <0.001), respectively. Thus, the need for RBC transfusion during hospitalization seems to be an independent descriptive factor associated with the long-term mortality of patients with ACS who did not undergo CABG, and its prominent association with decreased survival remained even after 1 year.

Patients' Hb levels were analyzed for several time points: on admission, nearest to the angiography date, at discharge, at 1 to 3 months, at 6 to 18 months, and at 1 to 4 years after hospitalization. Both highest and nadir-Hb concentrations during hospitalization were also recorded (Figure 3, Table 2). In our unmatched non-CABG cohort, the baseline anemic (as defined by World Health Organization standards) patients had a markedly increased mortality compared with nonanemic patients (45.8% [215/469] vs 21.4% [239/1,116], p <0.001). Nadir-Hb under 100 g/L during hospitalization was also associated with mortality when compared with nadir-Hb > 100 g/L (56.1% [97/173] vs 25.1% [341/1,360], p <0.001). RBC-transfused patients were more often anemic at baseline and had a deeper decline in Hb during hospitalization compared with their non–RBC-transfused counterparts (Table 2). This difference in Hb concentration between the groups remained throughout the follow-up period.

We found that 98.8% (84/85) and 22.4% (19/85) of RBC-transfused patients in our cohort had a nadir-Hb below 100 and 80 g/L, respectively. The strong correlation between nadir-Hb (g/L) under 100 and 80 g/L (Cramer's V 0.789, p <0.001 and 0.447, p <0.001, respectively) and transfusion treatment demonstrated it was not statistically feasible to include the nadir-Hb as a covariate in the multivariate survival analyses. Instead, we used the baseline anemia as a suitable candidate confounder both in the final multivariate analyses and in the logistic regression for propensity score matching. In a subgroup analysis, there was no significant difference in mortality between RBC-transfused patients with a nadir-Hb below versus over 80 g/L (57.9% [11/19] vs 59.1% [39/66], p = 0.926). Instead, multivariate subgroup analyses revealed that RBC transfusion increased mortality within both nonanemic (OS: HR 3.57, 95% CI 1.65 to 7.72, p = 0.001; 1YLS: HR 3.02, 95% CI 1.22 to 7.48, p = 0.017) and anemic (OS: HR 1.55, 95% CI 1.05 to 2.29, p = 0.028; 1YLS: HR 1.63, 95% CI 1.07 to 2.47, p = 0.023) patients.

Table 3
Multivariable predictors of mortality

	Unmatched cohort				Propensity score matched cohort			
	Overall survival		1-year landmark		Overall survival		1-year landmark	
	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
Red blood cell transfusion	1.91 (1.39 – 2.63)	<0.001	1.90 (1.34 – 2.69)	<0.001	2.49 (1.49 – 4.17)	0.001	2.54 (1.41 – 4.58)	0.002
Atrial fibrillation	1.98 (1.47 – 2.68)	<0.001	2.06 (1.50 – 2.85)	0.001	-	-	-	-
Prior myocardial infarction	1.50 (1.16 – 1.94)	0.002	1.54 (1.17 – 2.03)	0.002	-	-	-	-
Glomerular filtration rate < 60 ml/min/1.73 m^2	1.61 (1.24 – 2.10)	<0.001	1.60 (1.20 – 2.13)	0.001	-	-	-	-
Diabetes	1.61 (1.25 – 2.06)	<0.001	1.65 (1.26 – 2.15)	<0.001	-	-	-	-
Statins	0.43 (0.28 – 0.65)	<0.001	0.42 (0.26 – 0.67)	<0.001	-	-	-	-
3-artery disease	1.82 (1.42 – 2.34)	<0.001	1.73 (1.32 – 2.26)	<0.001	2.47 (1.47 – 4.16)	0.001	-	-
Age	1.07 (1.06 – 1.08)	<0.001	1.08 (1.06 – 1.09)	<0.001	1.05 (1.02 – 1.08)	0.001	1.07 (1.03 – 1.10)	<0.001
Lower limb vascular operation	-	-	-	-	5.73 (2.11 – 15.53)	0.001	6.72 (1.83 – 24.64)	0.004
Prior coronary artery bypass grafting	-	-	-	-	3.00 (1.60 – 5.62)	0.001	3.61 (1.69 – 7.70)	<0.001
Propensity score	-	-	-	-	0.94 (0.27 – 3.30)	0.277	2.25 (0.59 – 8.62)	0.238
Kidney disease	-	-	-	-	2.48 (1.19 – 5.18)	0.016	-	-
Nitrates	-	-	-	-	1.98 (1.21 – 3.22)	0.006	-	-
Diuretics	-	-	-	-	2.08 (1.24 – 3.49)	0.006	-	-

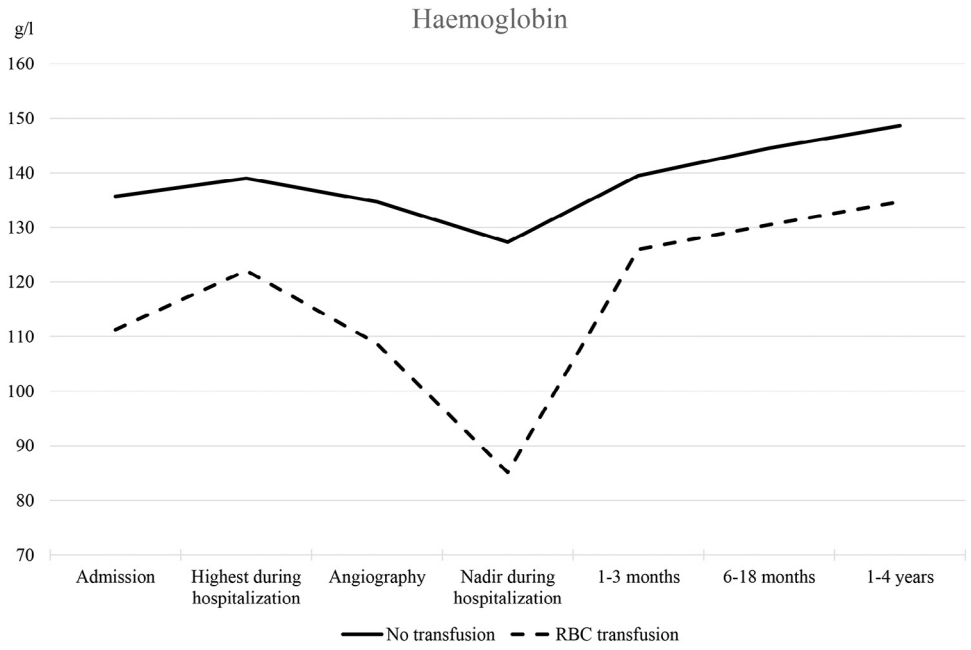

Figure 3. Mean hemoglobin values (g/L) at different time points during the follow-up.

The doubling in mortality for the RBC-transfused patients was analyzed further by examining patients' causes of death, and cancer (ICD-10 diagnosis C) was found to be interestingly overrepresented in RBC-transfused patients (15.3% [13/85] vs 4.1% [52/1,278], p <0.001). The Care Register for Health Care data were analyzed, and we found that 3.5% (3/85) versus 1.3% (16/1,278), p = 0.110, of RBC-transfused and non–RBC-transfused patients, respectively, had been diagnosed with cancer before their hospitalization. We further conducted a multivariate analysis with cancer mortality as an end point. In an age- and smoking-adjusted Cox model, excluding the patients who had a cancer diagnosis before hospitalization and transfusion, RBC transfusion was associated with increased cancer mortality (HR 2.89, 95% CI 1.44 to 5.77, p = 0.003). The incidence of new cancer diagnoses after the hospitalization, however, did not differ statistically between RBC-transfused and non–RBC-transfused patients (19.5% [16/82] vs 13.1% [165/1,262], p = 0.098, respectively). New malignant diagnoses, as well as cancer mortality, are listed in Table 2.

Discussion

The need for RBC transfusion in our cohort was strongly associated with increased mortality even after a 1-year follow-up for patients with ACS who did not undergo CABG. Moreover, after adjusting for several clinically and statistically appropriate covariates, RBC transfusion seemed to independently affect these patients' OS. Our study provides data for the longest follow-up (median 8.6 years), yet published and the most remarkable finding in our study is that the correlation between RBC transfusion and increased mortality stays strong throughout the follow-up. Previous studies have shown that RBC transfusion was associated with increased mortality for only up to 1 year after hospitalization.[14,16,22] All the RBC transfusion studies have acknowledged that RBC-transfused patients with ACS tend to be older and sicker than non–RBC-transfused patients. They are also more frequently anemic at baseline, have more underlying severe diseases such as diabetes and hypertension, have more severe coronary artery disease, and have worse renal function than their non–RBC-transfused counterparts.[7,13–16,23] Therefore, the question posed is as follows: Is there really a causal relationship between RBC transfusion and mortality, or is the transfusion per se actually an indicator of underlying sickness, such as anemia, and poorer overall health? These confounding issues were thoroughly addressed with both propensity score matching and Cox proportional hazards models as well as with the IPTW Cox model. Further large-scale randomized trials are, however, required to clarify if there is a causal relationship between RBC transfusion and increased mortality in patients with ACS. Nonetheless, we think that clinicians should try to identify patients at risk of bleeding early and exercise caution when deciding to treat patients with transfusion. We should utilize all measures available when trying to minimize the bleeding complications and the subsequent need of transfusion. These measures could entail recognizing the elderly or vulnerable patients who are prone to adverse effects earlier, reducing their dosages of anticoagulant and antithrombotic medications, using a radial instead of a femoral approach in interventions,[24] and considering other options for the correction of anemia. Previous studies have shown safe and efficacious results for intravenous iron infusion in treating patients who are in the vicious circle of chronic heart failure–renal anemia syndrome.[25] Further studies should be conducted to investigate the implication of this therapy on patients with ACS as well.

The association of RBC transfusion with cancer has scarcely been examined previously.[26] Interestingly, we found increased cancer mortality in the patients who received a transfusion in our cohort. We emphasize that this is merely a primary correlation in an observational study, but we

recommend investigating this topic further. We are also well aware that this association could be attributed to the potential for pre-existing undiagnosed malignancies to cause bleeding.

Obviously, we were not able to establish the causality of RBC transfusion and increased mortality from these observational findings. Patients who received the RBC transfusion were generally sicker, older, and in poorer conditions, which confounds the comparability of the unmatched groups to a certain extent. Propensity score matching and IPTW analysis were carried out to address this issue further. Given the observational study setting, the hidden bias formed by the possible unmeasured variables cannot be omitted, even with the matching and multiple regression that were performed. Unfortunately, the data on the history of bleeding and the indication for the transfusions were not conclusive for every RBC-transfused patient. However, our study benefited from an extensive but retrospective and nonstructural control of Hb levels throughout the follow-up. In conclusion, the need for RBC transfusion is strongly associated with increased long-term mortality in patients with ACS who did not undergo CABG even after 1 year. The causality and nature of this association remains unknown, but caution is warranted when treating patients with ACS with RBC transfusion. Further randomized trials are certainly needed to identify the true efficacy and safety of RBC transfusion for patients with ACS. We also found an association of RBC transfusion with increased cancer mortality, and we suggest investigating this topic further.

Disclosures

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Supplementary Data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.amjcard.2018.02.035.

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