

ORIGINAL ARTICLE

Identifying the Phenotypes of Sepsis that will Benefit from Red Blood Cell Transfusion Using Unsupervised Cluster Analysis

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SUMMARY

Background: Sepsis is a heterogeneous syndrome. Previous studies have shown controversial results of the effects of red blood cell transfusion (RBC) on the clinical outcomes of septic patients. This study aimed to identify the phenotypes of sepsis that will benefit from RBC transfusion.

Methods: Clinical data were extracted from the Medical Information Mart for Intensive Care III database. The study population included adult (age ≥ 18 years) septic patients with moderate non-bleeding anemia (hemoglobin ≤ 10 g/dL) within 24 hours after admission to the intensive care unit (ICU) between 2001 and 2012. After data pre-processing, partitioning around medoids function was used for unsupervised cluster analysis. We used Kaplan-Meier survival analysis and multivariable Cox proportional hazard models to explore the relationship between RBC transfusion and mortality.

Results: In total, 6,821 septic patients with moderate non-bleeding anemia within 24 hours after ICU admission, and 3,874 patients (56.8%) received RBC transfusion during their stay in the ICU. Using unsupervised cluster analysis, we identified three phenotypes of septic patients with moderate non-bleeding anemia: cluster A (n = 1,835) was characterized by advanced age and heart issues; cluster B (n = 3,043) was characterized by mild disease and relatively high hemoglobin levels; and cluster C (n = 1,943) was characterized by severe disease, low mean arterial pressure, bloodstream infection, coagulopathy, high lactate levels, and high mortality. Only for patients in cluster C, RBC transfusion exhibited protective effects in terms of the 14-day [hazard ratio (HR), 0.50; 95% confidence interval (CI), 0.41 - 0.61; $p < 0.001$], 28-day (HR, 0.61; 95% CI, 0.51 - 0.72; $p < 0.001$), and 90-day (HR, 0.67; 95% CI, 0.58 - 0.78; $p < 0.001$) mortality after adjusting the confounding variables.

Conclusions: Utilizing unsupervised cluster analysis, we identified three phenotypes of septic patients with moderate non-bleeding anemia who had different responses to RBC transfusion. In the future, randomized controlled trials about prognostic outcomes of RBC transfusions can focus on the specific phenotype of sepsis.

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Supplementary Tables and Figures

Table S1. Characteristics of patients who received or did not receive a red blood cell transfusion.

Characteristic	Overall n = 6,821	Transfusion n = 3,874	No transfusion n = 2,947	P *
Age (y), median (IQR)	69.15 (56.60 - 80.11)	68.66 (56.20 - 79.31)	69.83 (57.10 - 81.14)	< 0.001
Male, No. (%)	3,439 (50.4%)	2,030 (52.4%)	1,409 (47.8%)	< 0.001
Type of ICU, No. (%)				< 0.001
CCU	751 (11.0%)	448 (11.6%)	303 (10.3%)	
CSRU	1,149 (16.8%)	819 (21.1%)	330 (11.2%)	
MICU	3,350 (49.1%)	1,618 (41.8%)	1,732 (58.8%)	
SICU	991 (14.6%)	611 (15.7%)	380 (12.8%)	
TSICU	580 (8.5%)	378 (9.8%)	202 (6.9%)	
HR (/min), median (IQR) ^a	87.12 (76.87 - 98.39)	88.48 (78.45 - 99.46)	85.34 (75.07 - 96.63)	< 0.001
MAP (mmHg), median (IQR) ^a	73.75 (67.91 - 80.70)	73.90 (68.20 - 80.75)	73.56 (67.38 - 80.69)	0.059
RR (/min), median (IQR) ^a	18.98 (16.46 - 22.21)	18.71 (16.17 - 22.08)	19.33 (16.94 - 22.32)	< 0.001
SpO ₂ (%), median (IQR) ^a	97.57 (96.21 - 98.72)	97.83 (96.44 - 98.90)	97.24 (95.92 - 98.42)	< 0.001
SOFA, median (IQR)	5.00 (4.00 - 8.00)	6.00 (4.00 - 8.00)	5.00 (3.00 - 7.00)	< 0.001
LODS, median (IQR)	5.00 (3.00 - 7.00)	6.00 (4.00 - 8.00)	4.00 (3.00 - 6.00)	< 0.001
SAPS II, median (IQR)	41.00 (33.00 - 51.00)	43.00 (34.00 - 53.00)	39.00 (31.00 - 48.00)	< 0.001
Comorbidity, No. (%)				
Cerebrovascular disease	514 (7.5%)	303 (7.8%)	211 (7.2%)	0.328
Intracranial injury	191 (2.8%)	121 (3.1%)	70 (2.4%)	0.075
Cardiac disease	2,808 (41.2%)	1,690 (43.6%)	1,118 (37.9%)	< 0.001
Chronic kidney disease	1,385 (20.3%)	689 (17.8%)	696 (23.6%)	< 0.001
COPD/Asthma	1,365 (20.0%)	702 (18.1%)	663 (22.5%)	< 0.001
Liver disease	1,055 (15.5%)	717 (18.5%)	338 (11.5%)	< 0.001
Hematological disease	618 (9.1%)	387 (10.0%)	231 (7.8%)	0.002
Solid organ malignancies	1,010 (14.8%)	519 (13.4%)	491 (16.7%)	< 0.001
Organ transplant	132 (1.9%)	70 (1.8%)	62 (2.1%)	0.428
Peptic ulcer	159 (2.3%)	119 (3.1%)	39 (1.3%)	< 0.001
Laboratory findings				
APTT (s), median (IQR) ^b	37.20 (29.90 - 52.50)	38.90 (31.00 - 56.58)	35.00 (28.80 - 47.90)	< 0.001
PT (s), median (IQR) ^b	15.70 (14.00 - 18.50)	15.90 (14.20 - 18.70)	15.40 (13.70 - 18.20)	< 0.001
INR, median (IQR) ^b	1.50 (1.20 - 1.90)	1.50 (1.30 - 1.90)	1.40 (1.20 - 1.80)	< 0.001
Creatinine (mg/dL), median (IQR) ^b	1.30 (0.90 - 2.10)	1.30 (0.90 - 2.10)	1.30 (0.90 - 2.10)	0.788
Hematocrit (%), median (IQR) ^c	26.00 (23.20 - 28.00)	24.50 (22.00 - 26.87)	27.60 (25.80 - 29.00)	< 0.001
Hemoglobin (g/dL), median (IQR) ^c	8.70 (7.80 - 9.40)	8.30 (7.40 - 9.10)	9.20 (8.50 - 9.60)	< 0.001
Lactate (mmol/L), median (IQR) ^b	2.48 (1.71 - 3.67)	2.80 (1.90 - 4.20)	2.20 (1.51 - 3.00)	< 0.001
Platelets (10 ⁹ /L), median (IQR) ^c	166.00 (102.00 - 252.00)	143.00 (85.00 - 227.75)	192.00 (128.00 - 280.50)	< 0.001
WBC (10 ⁹ /L), median (IQR) ^b	13.00 (8.80 - 18.30)	13.50 (9.10 - 18.80)	12.40 (8.30 - 17.60)	< 0.001

Table S1. Characteristics of patients who received or did not receive a red blood cell transfusion (continued).

Characteristic	Overall n = 6,821	Transfusion n = 3,874	No transfusion n = 2,947	p*
Site of infection, No. (%)				
Respiratory tract	3,189 (46.8%)	1,832 (47.3%)	1,357 (46.0%)	0.320
Abdomen	1,851 (27.2%)	1,090 (28.1%)	761 (25.8%)	0.036
Urogenital tract	2,064 (30.2%)	1,128 (29.1%)	936 (31.8%)	0.020
Skin/Soft tissue	630 (9.2%)	369 (9.5%)	261 (8.9%)	0.367
Bloodstream	2,578 (37.8%)	1,520 (39.2%)	1,058 (35.9%)	0.005
Other ^d	1,302 (19.1%)	804 (20.8%)	498 (16.9%)	< 0.001
Site of operation, No. (%)				
Brain	178 (2.6%)	124 (3.2%)	54 (1.8%)	< 0.001
Lung	1,561 (22.8%)	1,115 (28.8%)	446 (15.1%)	< 0.001
Heart	1,452 (21.3%)	1,023 (26.4%)	429 (14.6%)	< 0.001
Great vessels	378 (5.6%)	326 (8.4%)	52 (1.8%)	< 0.001
Abdomen	2,351 (34.5%)	1,608 (41.5%)	743 (25.2%)	< 0.001
Bones/Joints	576 (8.4%)	405 (10.5%)	171 (5.8%)	< 0.001
Mechanical ventilation, No. (%)	3,738 (54.8%)	2,548 (65.8%)	1,190 (40.4%)	< 0.001
Renal replacement therapy, No. (%)	412 (6.0%)	246 (6.4%)	166 (5.6%)	0.238
Outcomes				
14 - day mortality, No. (%)	1,015 (14.8%)	521 (13.4%)	494 (16.8%)	< 0.001
28 - day mortality, No. (%)	1,468 (21.5%)	825 (21.3%)	643 (21.8%)	0.624
90 - day mortality, No. (%)	2,121 (31.1%)	1,239 (32.0%)	882 (29.9%)	0.074
ICU LOS, median (IQR)	4.00 (2.00 - 8.00)	6.00 (3.00 - 12.00)	3.00 (2.00 - 4.00)	< 0.001
Hospital LOS, median (IQR)	11.00 (7.00 - 20.00)	14.00 (9.00 - 24.00)	9.00 (5.00 - 14.00)	< 0.001

Abbreviations: IQR - interquartile range, ICU - intensive care unit, CCU - coronary care unit, CSRU - cardiac surgery recovery unit, MICU - medical intensive care unit, SICU - surgical intensive care unit, TSICU - trauma/surgical intensive care unit, HR - heart rate, MAP - mean arterial pressure, RR - respiratory rate, SpO₂ - pulse oxygen saturation, SOFA - sequential organ failure assessment, LODS - logistic organ dysfunction score, SAPS II - simplified acute physiology score II, COPD - chronic obstructive pulmonary disease, APTT - activated partial thromboplastin time, PT - prothrombin time, INR - international normalized ratio, WBC - white blood cell, LOS - length of stay.

* p - between transfusion and no transfusion.

^a - The mean value within 24 hours of ICU admission was calculated.

^b - The maximum value within 24 hours of ICU admission was calculated.

^c - The minimum value within 24 hours of ICU admission was calculated.

^d - The other sites of infection included central nervous system, bones, and unspecified site.

Table S2. Characteristics of patients between clusters.

Characteristic	Cluster A n = 1,835	Cluster B n = 3,043	Cluster C n = 1,943	P *
Age (y), median (IQR)	71.50 (60.55 - 80.03)	68.32 (55.54 - 80.38)	67.83 (54.94 - 79.90)	< 0.001
Male, No. (%)	928 (50.6%)	1,435 (47.2%)	1,076 (55.4%)	< 0.001
Type of ICU, No. (%)				< 0.001
CCU	287 (15.6%)	339 (11.1%)	125 (6.4%)	
CSRU	872 (47.5%)	147 (4.8%)	130 (6.7%)	
MICU	419 (22.8%)	1,808 (59.4%)	1,123 (57.8%)	
SICU	156 (8.6%)	461 (15.2%)	374 (19.3%)	
TSICU	101 (5.5%)	288 (9.5%)	191 (9.8%)	
HR (/minute), median (IQR) ^a	85.97 (78.14 - 94.16)	84.57 (74.15 - 95.96)	93.04 (81.17 - 105.79)	< 0.001
MAP (mmHg), median (IQR) ^a	74.57 (69.80 - 80.12)	74.64 (68.18 - 82.35)	71.28 (65.81 - 78.54)	< 0.001
RR (/minute), median (IQR) ^a	17.90 (15.80 - 20.38)	18.92 (16.65 - 22.00)	20.27 (17.34 - 23.95)	< 0.001
SpO ₂ (%), median (IQR) ^a	98.24 (97.09 - 99.09)	97.08 (95.86 - 98.21)	97.71 (96.07 - 98.94)	< 0.001
SOFA, median (IQR)	5.00 (4.00 - 7.00)	4.00 (3.00 - 5.00)	8.00 (6.00 - 11.00)	< 0.001
LODS, median (IQR)	5.00 (4.00 - 7.00)	4.00 (2.00 - 5.00)	8.00 (6.00 - 10.00)	< 0.001
SAPS II, median (IQR)	41.00 (34.00 - 49.00)	35.00 (29.00 - 42.00)	53.00 (44.00 - 63.00)	< 0.001
Comorbidity, No. (%)				
Cerebrovascular disease	168 (9.2%)	227 (7.5%)	119 (6.1%)	0.002
Intracranial injury	36 (2.0%)	105 (3.5%)	50 (2.6%)	0.007
Cardiac disease	1,337 (72.9%)	896 (29.4%)	575 (29.6%)	< 0.001
Chronic kidney disease	331 (18.0%)	632 (20.8%)	422 (21.7%)	0.013
COPD/Asthma	408 (22.2%)	660 (21.7%)	297 (15.3%)	< 0.001
Liver disease	113 (6.2%)	370 (12.2%)	572 (29.4%)	< 0.001
Hematological disease	110 (6.0%)	290 (9.5%)	218 (11.2%)	< 0.001
Solid organ malignancies	131 (7.1%)	551 (18.1%)	328 (16.9%)	< 0.001
Organ transplant	39 (2.1%)	60 (2.0%)	33 (1.7%)	0.623
Peptic ulcer	23 (1.3%)	70 (2.3%)	65 (3.3%)	< 0.001
Laboratory findings				
APTT (s), median (IQR) ^b	39.30 (31.50 - 56.13)	33.40 (28.20 - 45.25)	41.70 (32.65 - 61.25)	< 0.001
PT (s), median (IQR) ^b	15.40 (14.10 - 17.10)	15.00 (13.60 - 17.65)	17.40 (15.00 - 21.90)	< 0.001
INR, median (IQR) ^b	1.40 (1.30 - 1.70)	1.40 (1.20 - 1.71)	1.70 (1.40 - 2.40)	< 0.001
Creatinine (mg/dL), median (IQR) ^b	1.10 (0.80 - 1.60)	1.20 (0.80 - 1.80)	1.90 (1.20 - 3.15)	< 0.001
Hematocrit (%), median (IQR) ^c	24.00 (21.10 - 26.60)	27.30 (25.10 - 28.80)	25.40 (23.00 - 27.60)	< 0.001
Hemoglobin (g/dL), median (IQR) ^c	8.10 (7.20 - 9.00)	9.10 (8.50 - 9.60)	8.50 (7.75 - 9.20)	< 0.001
Lactate (mmol/L), median (IQR) ^b	2.70 (1.90 - 3.60)	2.10 (1.50 - 2.70)	3.54 (2.30 - 5.90)	< 0.001
Platelets (10 ⁹ /L), median (IQR) ^c	151.00 (107.00 - 214.00)	199.00 (128.00 - 288.00)	125.00 (67.00 - 220.00)	< 0.001
WBC (10 ⁹ /L), median (IQR) ^b	13.80 (10.40 - 17.90)	11.10 (7.60 - 15.90)	15.70 (9.60 - 22.50)	< 0.001
Site of infection, No. (%)				
Respiratory tract	806 (43.9%)	1,469 (48.3%)	914 (47.0%)	0.012
Abdomen	283 (15.4%)	793 (26.1%)	775 (39.9%)	< 0.001
Urogenital tract	612 (33.4%)	970 (31.9%)	482 (24.8%)	< 0.001

Table S2. Characteristics of patients between clusters (continued).

Characteristic	Cluster A n = 1,835	Cluster B n = 3,043	Cluster C n = 1,943	P*
Skin/Soft tissue	194 (10.6%)	283 (9.3%)	153 (7.9%)	0.016
Bloodstream	321 (17.5%)	852 (28.0%)	1,405 (72.3%)	< 0.001
Other ^d	396 (21.6%)	520 (17.1%)	386 (19.9%)	< 0.001
Site of operation, No. (%)				
Brain	43 (2.3%)	93 (3.1%)	42 (2.2%)	0.109
Lung	472 (25.7%)	551 (18.1%)	538 (27.7%)	< 0.001
Heart	1,172 (63.9%)	194 (6.4%)	86 (4.4%)	< 0.001
Great vessels	148 (8.1%)	102 (3.4%)	128 (6.6%)	< 0.001
Abdomen	293 (16.0%)	859 (28.2%)	1,199 (61.7%)	< 0.001
Bones/Joints	140 (7.6%)	270 (8.9%)	166 (8.5%)	0.313
Mechanical ventilation, No. (%)	1,616 (88.1%)	709 (23.3%)	1,413 (72.7%)	< 0.001
Renal replacement therapy, No. (%)	65 (3.5%)	135 (4.4%)	212 (10.9%)	< 0.001
Outcomes				
14 - day mortality, No. (%)	172 (9.4%)	308 (10.1%)	535 (27.5%)	< 0.001
28 - day mortality, No. (%)	260 (14.2%)	474 (15.6%)	734 (37.8%)	< 0.001
90 - day mortality, No. (%)	392 (21.4%)	757 (24.9%)	972 (50.0%)	< 0.001
ICU LOS, median (IQR)	5.00 (3.00 - 9.00)	3.00 (2.00 - 5.00)	6.00 (3.00 - 12.00)	< 0.001
Hospital LOS, median (IQR)	13.00 (9.00 - 19.00)	10.00 (6.00 - 16.00)	14.00 (7.00 - 26.00)	< 0.001

Abbreviations: IQR - interquartile range, ICU - intensive care unit, CCU - coronary care unit, CSRU - cardiac surgery recovery unit, MICU - medical intensive care unit, SICU - surgical intensive care unit, TSICU - trauma/surgical intensive care unit, HR - heart rate, MAP - mean arterial pressure, RR - respiratory rate, SpO₂ - pulse oxygen saturation, SOFA: sequential organ failure assessment, LODS - logistic organ dysfunction score, SAPS II - simplified acute physiology score II, COPD - chronic obstructive pulmonary disease, APTT - activated partial thromboplastin time, PT - prothrombin time, INR - international normalized ratio, WBC - white blood cell, LOS - length of stay.

* p - between clusters.

^a - The mean value within 24 hours of ICU admission was calculated.

^b - The maximum value within 24 hours of ICU admission was calculated.

^c - The minimum value within 24 hours of ICU admission was calculated.

^d - The other sites of infection included central nervous system, bones, and unspecified site.

Table S3. Multivariate adjusted hazard ratio of death due to red blood cell transfusion at 14 - day, 28 - day, and 90 - day intervals.

	14 - day mortality		28 - day mortality		90 - day mortality	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Overall	0.67 (0.58 - 0.78)	< 0.001	0.82 (0.73 - 0.93)	0.002	0.92 (0.83 - 1.02)	0.119
Cluster A	0.83 (0.58 - 1.18)	0.302	0.99 (0.73 - 1.33)	0.937	1.01 (0.79 - 1.30)	0.931
Cluster B	0.93 (0.72 - 1.21)	0.596	1.02 (0.83 - 1.25)	0.877	1.12 (0.96 - 1.32)	0.153
Cluster C	0.50 (0.41 - 0.61)	< 0.001	0.61 (0.51 - 0.72)	< 0.001	0.67 (0.58 - 0.78)	< 0.001

Abbreviations: CI - confidence interval.

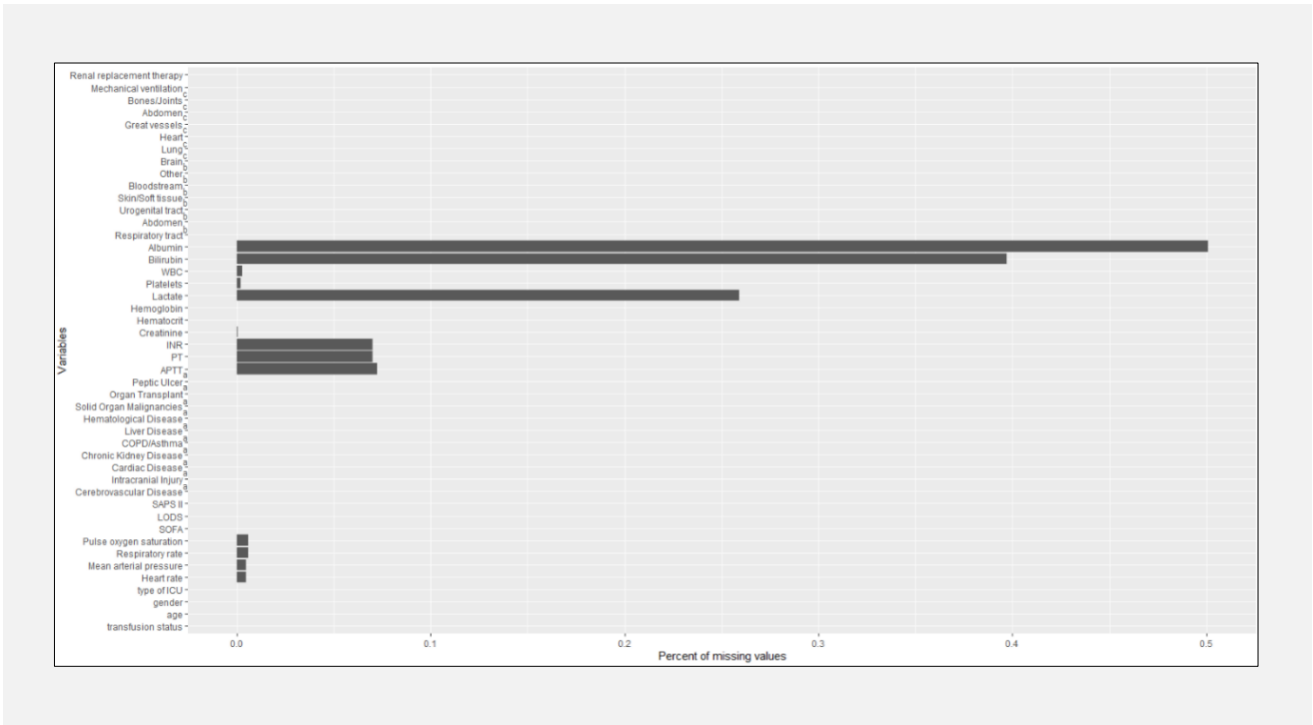


Figure S1. Percent of missing values for variables extracted for MIMIC III database (range: 0 - 1).

a: Comorbidity, b: Site of infection, c: Site of operation.

Abbreviations: ICU - intensive care unit, SOFA - Sequential Organ Failure Assessment, LODS - Logistic organ dysfunction score, SAPS II - Simplified acute physiology score II, COPD - Chronic obstructive pulmonary disease, APTT - Activated partial thromboplastin time, PT - Prothrombin time, INR - international normalized ratio, WBC - White blood cell.

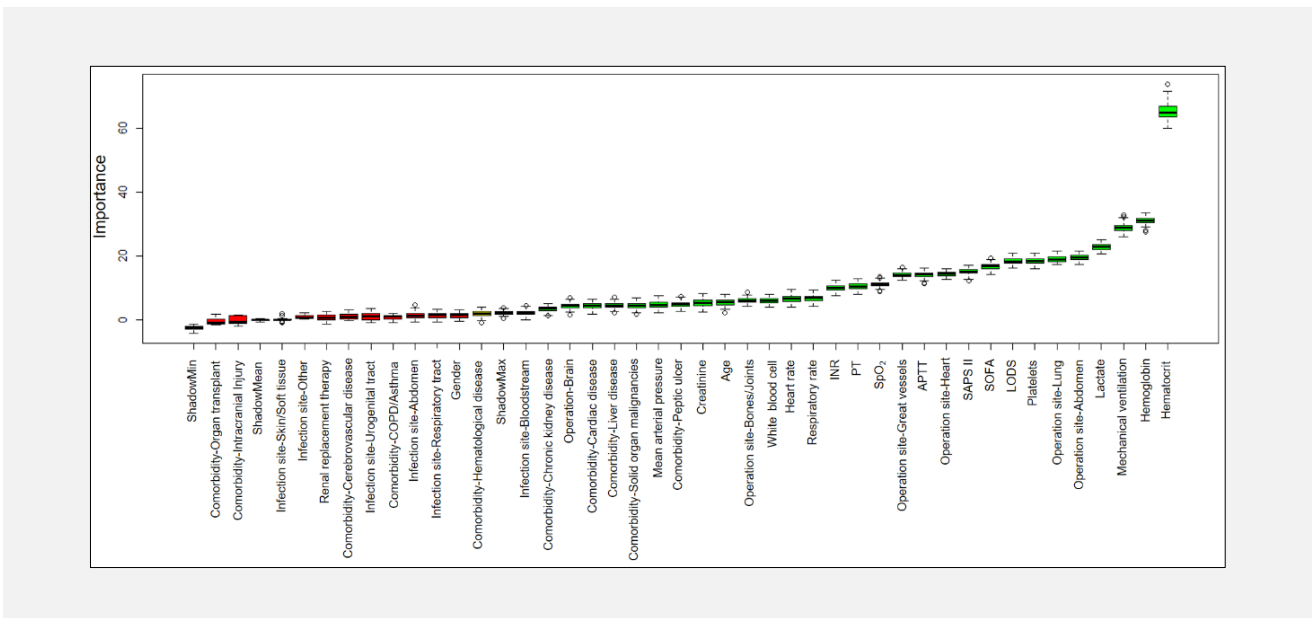


Figure S2. The importance of variables related to red blood cell transfusion according to Boruta algorithm.

Note: Blue boxplots represent the minimal, mean, and maximum Z score (importance) of shadow variables which are created by shuffling original ones. The Boruta algorithm compares the Z score between real variables and shadow variables. Variables that have significant lower Z score than their shadow ones are classified as unimportant variables which are represented by red boxplots. Yellow and green boxplots represent probably and definitely important variables which have higher Z score than their shadow ones.

Red Blood Cell Transfusion in Sepsis

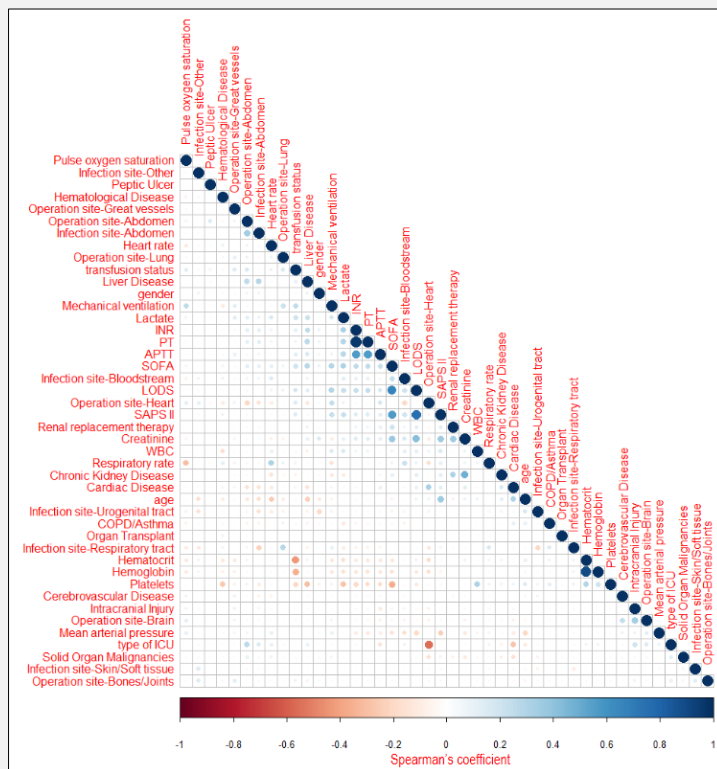


Figure S3. Spearman’s coefficient between variables.

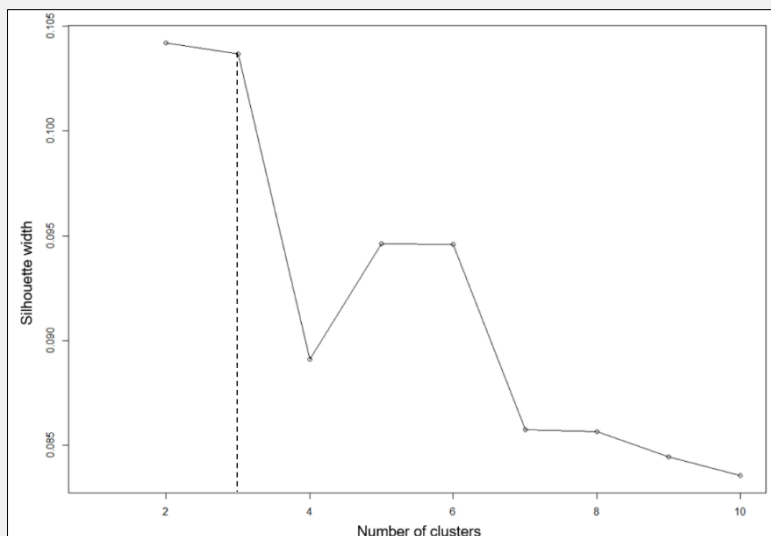


Figure S4. Silhouette coefficient plot.

Note: High silhouette coefficient reflects the rationality of individuals being grouped into their own cluster rather than others.