Machine learning for the prediction of augmented renal clearance (ARC)

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in patients with sepsis in critical care units.

Tong Wu[1,†], Ruo-Yu Zhuang[2,†], Yun-Zhe Wu[2,†], Xiao-Li Wang[1], Hong-ping Qu[1], Dan-Feng Dong[2], Yi-De Lu[2,*], Jing-yi Wu[1,*]

[1]Department of Critical Care Medicine, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China

[2]Department of laboratory medicine, Ruijin Hospital, Shanghai Jiaotong University School of Medicine

† These authors contributed equally to this work.

*Corresponding author. Author order was determined by work allocation.

Correspondence and requests for materials should be addressed to:

Jing-yi Wu; No.197, Ruijin ER Road, Shanghai 200025, China; +86-02164370045; E-mail: ajbriankevin@hotmail.com

and

Yi-De Lu; No.197, Ruijin ER Road, Shanghai 200025, China; +86-13641801889; E-mail: yidelu@sina.com

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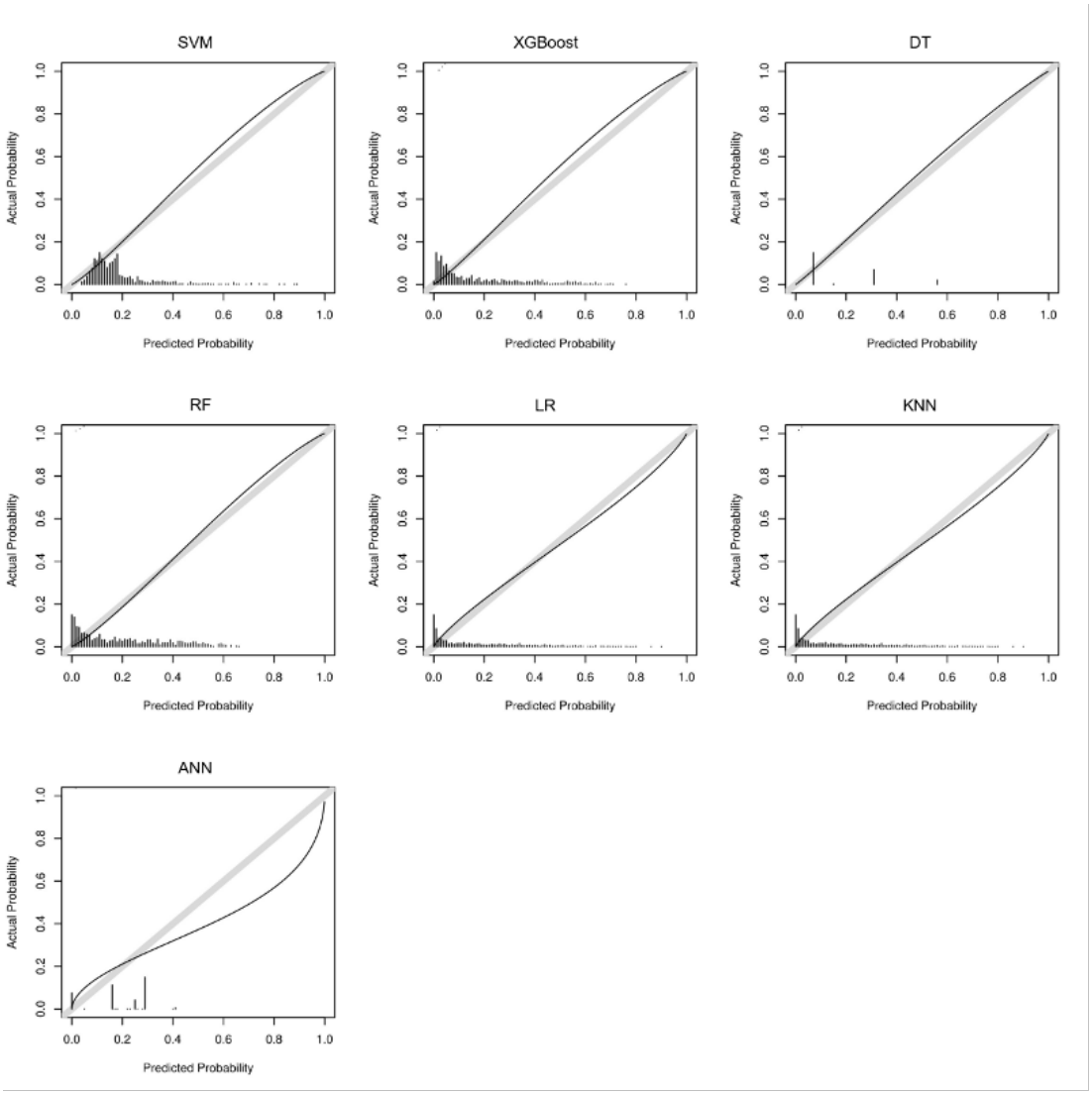

SFig 1. Calibration curves for the seven ML models in the validation set. SVM: support vector machine; XGBoost: Extreme Gradient Boosting; DT: Decision Tree; RF: Random Forest; LR: logistic regression; KNN, k-nearest neighbors; ANN: artificial neural network.

Variables		Overall (n = 2673)	Non-ARC (n = 2155)	ARC (n = 518)	*P*-value
Male, n (%)		1532 (57.3)	1251 (58.1)	281 (54.2)	0.128
Age, median [IQR]		67.00 [55.00, 77.00]	68.00 [57.50, 79.00]	58.00 [46.00, 71.00]	<0.001
Ethnicity, n (%)					0.005
	White	1790 (67.0)	1461 (67.8)	329 (63.5)	
	Black	254 (9.5)	216 (10.0)	38 (7.3)	
	Latino	100 (3.7)	81 (3.8)	19 (3.7)	

	Asian	67 (2.5)	52 (2.4)	15 (2.9)	
	Other	462 (17.3)	345 (16.0)	117 (22.6)	
Weight, median [IQR]		79.90 [66.20, 96.80]	80.00 [66.43, 97.50]	77.07 [65.60, 93.54]	0.038
Height, median [IQR]		170.00 [163.00, 178.00]	170.00 [161.00, 178.00]	168.00 [163.00, 178.00]	0.557
BMI, median [IQR]		27.70 [23.77, 32.67]	27.86 [24.07, 32.85]	26.84 [23.17, 31.80]	0.003
Surgery, n (%)		1678 (62.8)	1327 (61.6)	351 (67.8)	0.010
Trauma, n (%)		598 (22.4)	438 (20.3)	160 (30.9)	<0.001
CrCL, median [IQR]		45.34 [20.84, 103.66]	33.81 [17.57, 64.50]	196.56 [153.35, 265.97]	<0.001
Positive culture, n (%)		336 (12.6)	293 (13.6)	43 (8.3)	0.001
Infection sites					
Upper respiratory infection, n (%)		352 (13.2)	285 (13.2)	67 (12.9)	0.918
Pneumonia, n (%)		710 (26.6)	583 (27.1)	127 (24.5)	0.264
Abdominal infection, n (%)		270 (10.1)	226 (10.5)	44 (8.5)	0.204
Urinary infection, n (%)		588 (22.0)	493 (22.9)	95 (18.3)	0.029
Blood infection, n (%)		899 (33.6)	775 (36.0)	124 (23.9)	<0.001
Soft tissue infection, n (%)		43 (1.6)	33 (1.5)	10 (1.9)	0.558
CNS infection, n (%)		44 (1.6)	30 (1.4)	14 (2.7)	0.052
Other, n (%)		1086 (40.6)	844 (39.2)	242 (46.7)	0.002
Organ Dysfunction					
SOFA, median [IQR]		6.00 [4.00, 9.00]	7.00 [4.00, 9.00]	5.00 [3.00, 7.00]	<0.001
Vasopressor use, n (%)		1253 (46.9)	1044 (48.4)	209 (40.3)	0.001
Duration of vasopressor use, median [IQR]		18.62 [9.02, 23.68]	18.79 [9.54, 23.79]	16.83 [6.30, 22.40]	0.018
Max dosage of norepinephrine equivalent, median [IQR]		0.20 [0.10, 0.40]	0.20 [0.10, 0.40]	0.20 [0.10, 0.38]	0.827
Dopamine use, n (%)		134 (5.0)	117 (5.4)	17 (3.3)	0.044
Vasopressin use, n (%)		240 (9.0)	196 (9.1)	44 (8.5)	0.731
Norepinephrine use, n (%)		914 (34.2)	773 (35.9)	141 (27.2)	<0.001
Epinephrine use, n (%)		97 (3.6)	83 (3.9)	14 (2.7)	0.240
Phenylephrine use, n (%)		513 (19.2)	410 (19.0)	103 (19.9)	0.701
Mechanical ventilation, n (%)		1735 (64.9)	1354 (62.8)	381 (73.6)	<0.001

Urine-output, median [IQR]	1360.00 [792.00, 2260.00]	1275.00 [745.00, 2135.00]	1710.00 [1069.75, 2735.00]	<0.001
Comorbidities				
CCI, median [IQR]	5.00 [3.00, 8.00]	6.00 [4.00, 8.00]	4.00 [2.00, 5.00]	<0.001
Myocardial infarct, n (%)	433 (16.2)	378 (17.5)	55 (10.6)	<0.001
Congestive heart failure, n (%)	989 (37.0)	876 (40.6)	113 (21.8)	<0.001
Peripheral vascular disease, n (%)	311 (11.6)	285 (13.2)	26 (5.0)	<0.001
Cerebrovascular disease, n (%)	508 (19.0)	380 (17.6)	128 (24.7)	<0.001
Dementia, n (%)	95 (3.6)	85 (3.9)	10 (1.9)	0.024
Chronic pulmonary disease, n (%)	786 (29.4)	651 (30.2)	135 (26.1)	0.071
Rheumatic disease, n (%)	107 (4.0)	91 (4.2)	16 (3.1)	0.263
Peptic ulcer disease, n (%)	110 (4.1)	100 (4.6)	10 (1.9)	0.004
Mild liver disease, n (%)	581 (21.7)	497 (23.1)	84 (16.2)	0.001
Diabetes without complications, n (%)	679 (25.4)	594 (27.6)	85 (16.4)	<0.001
Diabetes with complications, n (%)	253 (9.5)	238 (11.0)	15 (2.9)	<0.001
Diabetes, n (%)	834 (31.2)	741 (34.4)	93 (18.0)	<0.001
Paraplegia, n (%)	164 (6.1)	119 (5.5)	45 (8.7)	0.010
Renal disease, n (%)	740 (27.7)	723 (33.5)	17 (3.3)	<0.001
Malignant cancer, n (%)	437 (16.3)	362 (16.8)	75 (14.5)	0.224
Severe liver disease, n (%)	324 (12.1)	288 (13.4)	36 (6.9)	<0.001
Metastatic solid tumor, n (%)	164 (6.1)	140 (6.5)	24 (4.6)	0.126
AIDS, n (%)	31 (1.2)	22 (1.0)	9 (1.7)	0.173
Vital signs				
HR_min, median [IQR]	74.00 [63.00, 89.00]	74.00 [63.00, 88.00]	75.00 [63.00, 92.00]	0.285
HR_max, median [IQR]	108.00 [93.00, 124.00]	108.00 [93.00, 124.00]	112.00 [96.00, 126.00]	0.008
SBP_min, median [IQR]	88.00 [79.00, 101.00]	87.00 [78.00, 100.00]	91.00 [81.00, 105.00]	<0.001
SBP_max, median [IQR]	147.00 [132.00, 164.00]	146.00 [132.00, 163.00]	149.00 [135.00, 166.00]	0.004
DBP_min, median [IQR]	45.00 [38.00, 53.00]	45.00 [37.00, 52.00]	48.00 [41.00, 58.00]	<0.001

DBP_max, median [IQR]	86.00 [75.00, 100.00]	85.00 [74.00, 98.00]	90.00 [78.00, 102.75]	<0.001
MBP_min, median [IQR]	58.00 [50.00, 66.00]	57.00 [49.00, 65.00]	61.00 [52.00, 70.00]	<0.001
MBP_max, median [IQR]	102.00 [91.00, 117.00]	101.00 [90.00, 115.25]	106.00 [95.00, 121.00]	<0.001
RR_min, median [IQR]	14.00 [11.00, 18.00]	14.00 [11.00, 18.00]	14.00 [12.00, 18.00]	0.483
RR_max, median [IQR]	28.00 [24.00, 33.00]	28.00 [24.00, 33.00]	28.00 [24.00, 32.75]	0.085
Temperature_min, median [IQR]	36.44 [36.00, 36.78]	36.44 [36.00, 36.72]	36.50 [36.06, 36.83]	0.003
Temperature_max, median [IQR]	37.44 [37.00, 38.06]	37.39 [37.00, 38.00]	37.67 [37.17, 38.28]	<0.001
SpO2_min, median [IQR]	93.00 [90.00, 96.00]	93.00 [90.00, 96.00]	94.00 [90.00, 96.00]	0.004
SpO2_max, median [IQR]	100.00 [100.00, 100.00]	100.00 [100.00, 100.00]	100.00 [100.00, 100.00]	0.747
Laboratory variables				
Glucose_min, median [IQR]	125.25 [104.00, 154.00]	126.00 [104.50, 155.50]	123.00 [103.50, 146.00]	0.049
Glucose_max, median [IQR]	170.00 [133.00, 227.00]	174.00 [135.00, 230.00]	159.00 [129.00, 212.00]	<0.001
pH_min, median [IQR]	7.36 [7.27, 7.43]	7.36 [7.27, 7.43]	7.37 [7.29, 7.43]	0.282
pH_max, median [IQR]	7.42 [7.37, 7.47]	7.42 [7.36, 7.46]	7.43 [7.38, 7.47]	0.019
PO2_min, median [IQR]	103.00 [72.00, 188.00]	102.00 [71.00, 188.00]	106.50 [74.25, 196.50]	0.086
PO2_max, median [IQR]	172.00 [113.00, 278.00]	169.00 [111.00, 272.50]	192.50 [124.25, 309.75]	0.002
PCO2_min, median [IQR]	37.00 [30.00, 45.00]	36.00 [29.00, 44.00]	38.00 [33.00, 49.00]	<0.001
PCO2_max, median [IQR]	43.00 [34.00, 53.00]	43.00 [34.00, 53.00]	43.00 [35.00, 53.00]	0.971
BE_min, median [IQR]	0.00 [-4.00, 7.00]	0.00 [-4.00, 9.00]	0.00 [-4.00, 3.00]	0.071
BE_max, median [IQR]	0.00 [-4.00, 2.00]	-1.00 [-5.00, 2.00]	0.00 [-3.00, 3.00]	<0.001
Total CO2_min, median [IQR]	22.00 [17.00, 27.00]	22.00 [17.00, 26.00]	24.00 [20.00, 27.00]	<0.001
Total CO2_max, median [IQR]	24.00 [15.00, 28.00]	23.00 [11.00, 27.00]	25.00 [21.00, 29.00]	<0.001
Cl_min, median [IQR]	104.00 [99.00, 107.50]	104.00 [99.00, 108.00]	103.00 [100.00, 107.38]	0.924
Cl_max, median [IQR]	106.00 [102.00, 110.00]	106.00 [102.00, 110.00]	106.00 [102.00, 111.00]	0.238
Ca_min, median [IQR]	6.70 [4.62, 8.40]	7.10 [4.66, 8.40]	5.16 [4.53, 8.20]	<0.001

Ca_max, median [IQR]	7.20 [4.88, 8.60]	7.50 [4.90, 8.70]	5.30 [4.82, 8.50]	0.001
K_min, median [IQR]	4.20 [3.75, 4.65]	4.20 [3.80, 4.70]	3.90 [3.60, 4.40]	<0.001
K_max, median [IQR]	4.50 [4.10, 5.10]	4.60 [4.15, 5.20]	4.30 [3.95, 4.80]	<0.001
Na_min, median [IQR]	138.00 [134.50, 141.00]	138.00 [134.50, 141.00]	138.00 [135.00, 141.00]	0.426
Na_max, median [IQR]	140.00 [136.00, 143.00]	140.00 [136.00, 143.00]	140.00 [137.00, 143.00]	0.135
AG_min, median [IQR]	15.00 [13.00, 18.00]	16.00 [13.00, 18.00]	14.00 [12.00, 17.00]	<0.001
AG_max, median [IQR]	17.00 [15.00, 20.00]	17.00 [15.00, 20.00]	16.00 [14.00, 19.00]	<0.001
BUN_min, median [IQR]	26.00 [16.00, 44.00]	30.00 [19.00, 49.00]	16.00 [12.00, 21.00]	<0.001
BUN_max, median [IQR]	29.00 [18.00, 47.00]	33.00 [22.00, 52.00]	17.00 [13.00, 23.00]	<0.001
Creatinine_min, median [IQR]	1.30 [0.90, 1.90]	1.40 [1.00, 2.10]	0.90 [0.70, 1.10]	<0.001
Creatinine_max, median [IQR]	1.40 [1.00, 2.10]	1.60 [1.10, 2.30]	0.90 [0.70, 1.20]	<0.001
ALT_min, median [IQR]	30.00 [15.00, 73.00]	30.00 [16.00, 73.00]	28.00 [14.00, 66.75]	0.090
ALT_max, median [IQR]	30.00 [18.00, 65.00]	30.00 [18.00, 65.50]	30.00 [17.00, 65.00]	0.870
ALP_min, median [IQR]	106.00 [66.00, 182.00]	108.00 [69.00, 182.00]	94.00 [59.00, 182.00]	0.010
ALP_max, median [IQR]	107.00 [69.00, 162.00]	107.00 [71.50, 162.00]	101.00 [62.00, 158.75]	0.016
AST_min, median [IQR]	49.00 [27.00, 115.00]	50.00 [27.00, 117.50]	48.00 [26.25, 110.00]	0.563
AST_max, median [IQR]	53.00 [28.00, 134.00]	54.00 [28.00, 138.00]	50.00 [27.00, 116.75]	0.437
TB_min, median [IQR]	0.70 [0.40, 1.50]	0.70 [0.40, 1.60]	0.70 [0.40, 1.20]	0.001
TB_max, median [IQR]	1.20 [0.50, 13.90]	1.30 [0.50, 11.20]	1.20 [0.50, 13.90]	0.664
Hct_min, median [IQR]	32.60 [27.85, 37.90]	32.00 [27.30, 37.20]	35.50 [30.90, 40.88]	<0.001
Hct_max, median [IQR]	34.30 [29.95, 39.00]	33.50 [29.50, 38.35]	36.85 [32.70, 41.80]	<0.001
Hb_min, median [IQR]	10.70 [9.10, 12.50]	10.40 [8.90, 12.20]	11.78 [10.11, 13.50]	<0.001
Hb_max, median [IQR]	11.20 [9.70, 12.90]	10.95 [9.55, 12.65]	12.30 [10.80, 13.99]	<0.001
PLT_min, median [IQR]	209.00 [140.00, 286.00]	204.00 [134.00, 283.50]	225.00 [162.00, 301.75]	<0.001

PLT_max, median [IQR]	225.00 [154.00, 301.00]	221.00 [150.00, 297.00]	235.00 [174.25, 309.75]	<0.001
WBC_min, median [IQR]	12.40 [8.70, 16.90]	12.40 [8.60, 16.90]	12.35 [9.00, 16.67]	0.893
WBC_max, median [IQR]	14.50 [10.20, 19.70]	14.60 [10.20, 19.90]	14.00 [10.20, 19.25]	0.354
RBC_min, median [IQR]	3.64 [3.06, 4.23]	3.55 [3.00, 4.14]	3.97 [3.41, 4.57]	<0.001
RBC_max, median [IQR]	3.79 [3.29, 4.35]	3.71 [3.22, 4.27]	4.14 [3.64, 4.67]	<0.001
RDW_min, median [IQR]	15.10 [13.90, 17.10]	15.40 [14.10, 17.35]	14.20 [13.30, 15.60]	<0.001
RDW_max, median [IQR]	15.40 [14.10, 17.40]	15.70 [14.40, 17.70]	14.40 [13.50, 15.80]	<0.001
Basophils_min, median [IQR]	0.03 [0.00, 0.06]	0.03 [0.00, 0.06]	0.03 [0.01, 0.08]	0.003
Basophils_max, median [IQR]	0.02 [0.00, 0.05]	0.02 [0.00, 0.05]	0.02 [0.00, 0.05]	0.109
Eosinophils_min, median [IQR]	0.02 [0.00, 0.11]	0.02 [0.00, 0.11]	0.02 [0.00, 0.12]	0.403
Eosinophils_max, median [IQR]	0.02 [0.00, 0.11]	0.02 [0.00, 0.11]	0.02 [0.00, 0.11]	0.591
Lymphocytes_min, median [IQR]	1.12 [0.68, 1.66]	1.10 [0.66, 1.64]	1.15 [0.78, 1.77]	0.002
Lymphocytes_max, median [IQR]	1.15 [0.70, 1.87]	1.14 [0.68, 1.85]	1.21 [0.76, 2.04]	0.004
Monocytes_min, median [IQR]	0.52 [0.24, 0.95]	0.53 [0.25, 0.95]	0.49 [0.23, 0.97]	0.375
Monocytes_max, median [IQR]	0.73 [0.40, 1.51]	0.73 [0.40, 1.48]	0.71 [0.39, 1.68]	0.812
Neutrophils_min, median [IQR]	8.47 [4.33, 13.74]	8.65 [4.41, 14.00]	7.80 [4.06, 12.52]	0.021
Neutrophils_max, median [IQR]	10.16 [5.46, 16.00]	10.20 [5.50, 16.07]	10.00 [5.44, 15.27]	0.436
INR_min, median [IQR]	1.30 [1.10, 1.70]	1.30 [1.20, 1.80]	1.20 [1.10, 1.40]	<0.001
INR_max, median [IQR]	1.40 [1.20, 2.00]	1.50 [1.20, 2.10]	1.30 [1.10, 1.50]	<0.001
PT_min, median [IQR]	14.60 [12.80, 19.00]	14.90 [13.00, 19.80]	13.60 [12.20, 15.60]	<0.001
PT_max, median [IQR]	15.50 [13.20, 21.40]	16.00 [13.45, 22.40]	14.30 [12.60, 17.08]	<0.001
PTT_min, median [IQR]	32.20 [27.90, 40.80]	32.70 [28.15, 42.05]	30.20 [26.83, 36.77]	<0.001
PTT_max, median [IQR]	35.30 [29.20, 52.60]	36.00 [29.50, 53.65]	32.80 [28.10, 45.25]	<0.001

Table S1. Baseline characteristics of septic patients with or without ARC within 7 days after admission to ICU. ICU: Intensive care unit; LOS: Lengths of stay; ARC: Augmented renal clearance; IQR: Interquartile range; min: minimum; max: maximum; BMI: Body mass index; CrCl: Creatinine clearance; CNS: Central nervous system; SOFA: Sepsis-related organ failure assessment; CCI: Charlson comorbidity index; AIDS: Acquired immune deficiency syndrome; HR: Heart rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MBP: Mean blood pressure; RR: Respiratory rate; SpO2: Percutaneous arterial oxygen saturation; PO2: Partial pressure of oxygen; PCO2: Partial pressure of carbon dioxide; BE: Base excess; Hct: Hematocrit; Hb: Hemoglobin; PLT: Platelet count; WBC: White blood cell count; RBC: Red blood cell count; RDW: Red blood cell distribution width; Cl: Serum chloride; Ca: Serum calcium; K: Serum potassium; Na: Serum sodium; AG: Anion gap; BUN: Blood urine nitrogen; INR: International normalized ratio; PT: Prothrombin time; APTT: Activated partial thromboplastin time; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; AST: Aspartate transaminase; TB: Total bilirubin.

Outcomes	Overall (n = 2673)	Non-ARC (n = 2155)	ARC (n = 518)	*P*-value
ICU mortality, n (%)	520 (19.5)	456 (21.2)	64 (12.4)	<0.001
In-hospital mortality, n (%)	704 (26.3)	616 (28.6)	88 (17.0)	<0.001
28-d mortality, n (%)	757 (28.3)	668 (31.0)	89 (17.2)	<0.001
ICU LOS, median [IQR]	7.03 [4.22, 12.46]	6.68 [4.04, 11.62]	9.64 [5.42, 15.54]	<0.001
hospital LOS, median [IQR]	14.00 [9.00, 23.00]	13.00 [8.00, 22.00]	16.50 [11.00, 26.00]	<0.001
ICU mortality, n (%)	520 (19.5)	456 (21.2)	64 (12.4)	<0.001
In-hospital mortality, n (%)	704 (26.3)	616 (28.6)	88 (17.0)	<0.001
28-d mortality, n (%)	757 (28.3)	668 (31.0)	89 (17.2)	<0.001

Table S2. Clinical outcomes of septic patients with or without ARC within 7 days after admission to ICU. ICU: Intensive care unit; LOS: Lengths of stay; ARC: Augmented renal clearance; IQR: Interquartile range.

Serum concentration of vancomycin	Overall (n = 1617)	Non-ARC (n = 1298)	ARC (n = 319)	*P*-value
Serum concentration of Vancomycin, median [IQR]	18.00 [13.00, 22.00]	19.00 [14.00, 22.00]	15.00 [11.00, 19.00]	<0.001
Minimum of serum concentration of Vancomycin, median [IQR]	13.00 [9.00, 17.00]	13.00 [10.00, 18.00]	11.00 [7.00, 14.00]	<0.001
Maximum of serum concentration of Vancomycin, median [IQR]	22.00 [15.00, 28.00]	23.00 [16.00, 29.00]	19.00 [13.00, 24.50]	<0.001

Table S3. Plasma concentration of vancomycin during antimicrobial therapy for septic patients administered with vancomycin in ICU. ICU: Intensive care unit; IQR: Interquartile range.