

Table S1. Relevant studies about 28-day mortality prediction for sepsis patients.

Authors	Title	Dataset	Methodology	Predictors	Outcome	Sepsis	AUROC
Masson, S. et al.	Presepsin (soluble CD14 subtype) and procalcitonin levels for mortality prediction in sepsis: data from the Albumin Italian Outcome Sepsis trial	A multicentre, randomised Albumin Italian Outcome Sepsis trial, 100 patients	Cox regression model	Presepsin level, procalcitonin level and some covariates	28-day/ICU/90-day mortality	Sepsis-2	
Fang W-F et al.	Development and validation of immune dysfunction score to predict 28-day mortality of sepsis patients	Sepsis patients admitted to ICU at a hospital in Taiwan, 151 patients	LR	Monocyte HLA-DR ⁺ expression, plasma G-CSF [*] level, plasma IL ⁻¹⁰ level, and serum SeMo ⁺ ratio	28-day mortality	Sepsis-3	0.85 (0.75-0.94)
Jau-Woei Perng et al.	Mortality Prediction of Septic Patients in the Emergency Department Based on Machine Learning	Sepsis patients admitted to ICU at a hospital in Taiwan, 42,220 patients	RF, KNN, SVM, SoftMax	Clinical variables (53) demographic data, vital signs, and laboratory results	72-hours/28-day in-hospital mortality	Sepsis-2	72h: RF(0.88) SVM (0.93) KNN(0.83) SoftMax(0.91) 24d: RF(0.79) SVM(0.93) KNN(0.84) SoftMax(0.93)
Nianzong Hou et al.	Predicting 30-days mortality for MIMIC-III patients with sepsis-3: a machine learning approach using XGboost	MIMIC-III, 4,559 patients	LR, SAPS-II score, XGBoost	demographics, vital signs, laboratory tests, fluid balance and vital status	30-day mortality	Sepsis-3	LR 0.82 (0.8-0.84) SAPS-II 0.80 (0.78-0.81) XGBoost 0.86 (0.84-0.88)

Abbreviations: ICU Intensive Care Unit, LR Logistic regression, RF Random forest, KNN K-nearest neighbor, SVM Support vector machine

Table S2. Biomarker distribution of the different subgroups.

Biomarkers (Median(IQR))	Total	Sepsis-1[†] (SIRS score≥2)	Sepsis-3^{††} (ΔSOFA≥2)	Septic Shock (ΔSOFA≥2+ Lactate>18 mg/dL)	Septic Shock (ΔSOFA≥2+ Lactate>18 mg/dL)+ Vasopressor usage
Numbers (%)	555 (100)	418 (75.32)	101 (18.20)	58 (10.45)	7 (1.26)
Procalcitonin (ng/mL)	0.59 (0.1-5.98)	0.79 (0.13-7.13)**	3.27 (0.73-20.06)***	6.01 (1.06-79.72)***	200 (28.90-200)***
Lactate (mg/dL)	14.7 (10.7-22.20)	15.3 (10.9-23.35)*	20 (13.23-30.05)***	28.4 (22.30-39.80)***	36.5 (24.9-68.65)***
C reactive protein (mg/L)	88.5 (40.60-160.94)	94 (37.84-164.72)	121.1 (59.60-172.5)**	115.52 (57.92-196.93)*	212.06 (138.72-249.95)**
D-dimer (ng/mL)	1295 (556.75-2858)	1370 (605.5-3054)**	2168 (1103-6673.75)***	2681 (1452-10000)***	6149 (2367.5-10000)**
IL-6 (pg/mL)	78.71 (41.79-148.76)	82.63 (42.28-161.97)*	114.46 (46.28-227.83)**	159.08 (56.37-253.25)**	175.33 (106.92-243.75)
IL-8 (pg/mL)	5.29 (2.61-13.49)	5.70 (2.79-14)	6.95 (3.33-14.00)	11.32 (4.25-19.47)**	14 (10.54-26.14)
IL-10 (pg/mL)	0.95 (0.10-3.25)	1.20 (0.14-3.55)**	1.15 (0.31-3.54)	1.89 (0.38-5.95)**	6.32 (3.34-8.78)*
TNF-α (pg/mL)	22.94 (14.7-35.30)	22.59 (14.67-34.46)	23.48 (17.08-34.53)	23.79 (17.63-38.5)	33.05 (27.-39.09)
IFN-γ (pg/mL)	0.065 (0.065-0.12)	0.065 (0.065-0.12)	0.065 (0.065-0.2)***	0.09 (0.065-0.2)***	0.13 (0.065-0.2)
Angiopoietin-2 (pg/mL)	827.01 (404.66-1510.85)	842.93 (408.63-1571.53)	1219.78 (645.88-1723.31)*	1258.62 (653.05-1805.59)*	878.65 (878.65-878.65)
Pantraxin-3 (ng/mL)	1.20 (0.60-2.29)	1.30 (0.65-2.51)***	1.30 (0.71-2.49)	1.91 (0.96-3.34)***	2.14 (1.53-2.72)
sCD14 (ug/mL)	2.27 (1.86-2.70)	2.21 (1.84-2.68)	2.43 (1.99-2.85)**	2.37 (1.98-2.88)	2.39 (1.87-3.38)
sCD64 (ng/mL)	86.55 (47.93-133.73)	93.15 (53.08-136.95)**	119.57 (80.74-180.49)***	151.39 (81.92-187.98)***	145.44 (98.22-189.28)
sCD-163 (ng/mL)	150.94 (104.26-251.28)	150.99 (104.26-243.60)	172.99 (110.45-257.13)	190.16 (146.04-291.24)	275.26 (257.13-310.06)
Triggering receptor expressed on myeloid cells 1 (pg/mL)	276.72 (9.49-514.32)	295.09 (9.49-538.20)	334.26 (234.12-492.09)	367.46 (241.38-564.07)	793.18 (638.27-849.46)*
Intercellular Adhesion Molecule 1 (ng/mL)	178.69 (103.61-277.12)	184.32 (109.84-292.34)**	226.30 (137.69-343.71)**	256.81 (142.45-339.68)*	244.1 (174.96-329.58)
Vascular cell adhesion protein 1 (ng/mL)	1.76 (1.17-2.65)	1.76 (1.25-2.59)	2.48 (1.49-3.60)***	2.68 (1.54-3.94)***	4.19 (3.51-4.62)**
E-selectin (ng/mL)	57.09 (37.01-101.49)	62.78 (39.28-106.85)**	70.11 (45.60-115.98)*	78.63 (43.21-116.17)	78.63 (51.05-150.80)
P-selectin (ng/mL)	52.34 (38.74-66.03)	54.39 (40.15-67.43)***	49.85 (38.95-69.57)	59.56 (39.21-70.62)	65.61 (52.70-75.62)
Procalcitonin (ng/mL)	0.59 (0.1-5.98)	0.79 (0.13-7.13)**	3.27 (0.73-20.06)***	6.01 (1.06-79.72)***	200 (28.90-200)***

Note: * P < 0.05, **P < 0.01, and *** P-value < 0.001 represent the difference between Sepsis-1, Sepsis-3, and septic shock compared to the corresponding control group.

Table S3. Comparison of level of sepsis-related novel biomarkers between the survivors and the in-hospital mortality groups.

Biomarkers Median (IQR)	Survivor(n=510)	Death(n=45)	<i>p</i> -value
IL-6 (pg/mL)	76.09 (41.71-147.08)	116.83 (47.44-265.48)	0.084
IL-8 (pg/mL)	5.07 (2.43-12.14)	13.65 (5.94-17.52)	<0.001
IL10 (pg/mL)	0.93 (0.10-3.08)	2.04 (0.71-5.04)	0.002
Angiopoetin-2 (pg/mL)	814.70 (407.61-1472.72)	1216.00 (371.96-1938.29)	0.258
Pantraxin (ng/mL)	1.18 (0.59-2.20)	1.57 (1.05-2.68)	0.019
sCD14 (ng/mL)	2.25 (1.86-2.68)	2.35 (1.85-2.85)	0.507
sCD64 (ng/mL)	84.60 (47.85-132.33)	96.92 (71.94-164.77)	0.061
sCD163 (ng/mL)	148.13 (103.56-236.43)	227.10 (136.54-324.85)	0.002
TREM1 (pg/mL)	267.16 (6.99-495.36)	452.8 (230.76-880.05)	0.001
ICAM1(ng/mL)	165.13 (100.56-268.18)	226.38 (181.11-355.87)	0.001
VCAM1 (ug/mL)	1.74 (1.16-2.55)	2.32 (1.56-3.00)	0.011
E-selectin (ng/mL)	56.99 (36.54-101.12)	60.81 (45-103.41)	0.387
P-selectin (ngr/mL)	51.43 (38.56-64.95)	61.19 (45.02-77.02)	0.034

TNF- α : tumor necrosis factor-alpha, IL-6: interleukin-6, IL-8: interleukin-8, IL-10: interleukin-10 and IFN- γ : interferon-gamma, sCD14: soluble cluster of differentiation-14, sCD64: soluble cluster of differentiation-64, sCD163: soluble cluster of differentiation-163, TREM-1: triggering receptor expressed on myeloid cells-1, ICAM-1: intercellular adhesion molecule-1 and VCAM-1: vascular cell adhesion protein-1.

Table S4. Total included features.

Number	Features
1	Age
2	temperature
3	Pulse centering value of 100
4	Systolic blood pressure centering value of 120
5	Diastolic blood pressure centering value of 75
6	Respiratory rate centering value of 18
7	oxyhemoglobin saturation by pulse oximetry
8	Mean arterial pressure centering value of 75
9	Glasgow Coma Scale

10	Angiopoietin-2 normalization
11	IL-6 normalization
12	TNF-a normalization
13	sCD163 normalization
14	IL-10 normalization
15	Pentraxin-3 normalization
16	normalization
17	normalization
18	CD14 normalization
19	TREM-1 normalization
20	CD64 normalization
21	ICAM-1 normalization
22	E-selectin normalization
23	P-selectin normalization
24	VCAM-1 normalization
25	Fasting Blood Glucose centering value of 180
26	Procalcitonin
27	C Reactive Protein
28	Lactate
29	Albumin
30	APTT centering value of 30
31	Prothrombin
32	INR
33	Bilirubin
34	BUN
35	AST
36	Phosphorous centering value of 3
37	Troponin-I
38	D-dimer
39	Cortisol
40	Calcium centering value of 8.75
41	Chloride
42	Uric Acid
43	C3
44	Protein C centering value of 75
45	pO2
46	SAT
47	HCO3 centering value of 25
48	pCO2
49	pH
50	Total CO2
51	ABE
52	AaDO2
53	FiO2
54	SBC
55	SBE
56	FDP
57	BAND
58	Serum Creatinine
59	Eosinophils
60	Hemoglobin
61	Hematocrit
62	MCHC
63	MCV
64	Platelet
65	Red Blood Cell
66	RDW

67	White Blood Cell centering value of 15
68	Potassium
69	Sodium
70	high blood pressure
71	Asthma
72	Gout
73	Parkinson
74	HIV
75	Stroke
76	Allergy
77	myocardial infarction
78	Congestive Heart Failure
79	Peripheral Vascular Disease
80	Cerebrovascular Disease
81	Dementia
82	Chronic Pulmonary Disease
83	Rheumatologic Disease
84	Peptic Ulcer Disease
85	Mild Liver Disease
86	Hemiplegia or paraplegia
87	Renal Disease
88	Leukemia
89	Lymphoma
90	Moderate or Severe Liver Disease
91	Metastatic Solid Tumor
92	Tumor
93	Chronic Kidney Disease
94	Carrier
95	Fatty Liver
96	Cirrhosis Liver
97	Liver Disease
98	Chronic Obstructive Pulmonary Disease
99	Any Malignancy
100	Diabetes mellitus
101	Respiratory infection
102	Urology infection
103	Skin infection
104	Abdominal infection
105	Central nervous system
106	Musculoskeletal infection
107	Other infection
108	Cardiovascular dysfunction
109	Respiratory dysfunction
110	Gastrointestinal tract
111	Renal dysfunction
112	Hepatic dysfunction
113	Neurologic dysfunction
114	Metabolic dysfunction
115	Hematologic dysfunction
116	Sequential Organ Failure Assessment (SOFA) Score
117	Sepsis-3, SOFA Score \geq 2
118	Septic shock , SOFA Score \geq 2 \geq 2 and Lactate $>$ 18
119	Body aches
120	Muscle ache
121	Convulsion
122	General Weak
123	Chills

124	Shaking Chill
125	Cyanosis
126	Fever
127	Sweat
128	No sweat
129	Dry Lips
130	Thirsty
131	Cold extremity
132	Malaise
133	Drowsy
134	Syncope
135	Confusion
136	Tachycardia
137	Agitation
138	acute confuse
139	Fluctuating confuse
140	Inattention
141	Disorganized think
142	Urine frequency
143	Oliguria
144	Hematuria
145	Difficulty urinating
146	Dysuria
147	Flan pain
148	Headache
149	Dizziness
150	Sore throat
151	Chest tightness
152	Dyspnea
153	Chest pain
154	Neck pain
155	Nasal congestion
156	Sneezing
157	Runny nose
158	Dry cough
159	Productive cough
160	Sputum
161	Hemoptysis
162	Abdominal diet
163	Abdominal pain
164	Diarrhea
165	Constipation
166	Nausea
167	Vomit
168	Anorexia
169	Jaundice
170	Hypotension
171	lactate higher
172	Creatinine over 2
173	Bilirubin over 2
174	Platelet less than 100
175	INR over 15
176	Male
177	an infiltrate on chest imaging
178	chest X-ray with consolidation from pneumonia
179	pneumonia patch
180	pulmonary edema

181	hazy shadow on chest x ray
182	Pneumonia
183	Upper respiratory tract infection
184	Patient older than 65 years old
185	Lower respiratory infection
186	Patient is from a nursing home
187	Mental status is altered
188	Granulocytic bands >5% of WBC
189	Platelet count below 150,000
190	Shock from sepsis
191	Hypoxia or tachypnea
192	Terminal illness with possible death in 1 month
193	Mortality in emergency department sepsis score
194	Temperature >38°C or < 36°C
195	Heart rate > 90
196	Respiratory rate > 20
197	WBC > 12,000/mm ³ or < 4,000/mm ³
198	SIRS score
199	Altered Mental Status
200	Dopamine <5 or dobutamine (any dose)
201	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1b
202	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1b
203	Respiratory System
204	Nervous System
205	Cardio Vascular System
206	Liver System
207	Coagulation System
208	Renal System
209	Vasopressor
210	Bacteremia
211	Intensive care unit
212	Severe sepsis
213	Chills
214	Hypothermia (temperature< 36°C)
215	Red blood cell volume distribution width >14.5%
216	Anemia (RBC counts < 4 million/μL)
217	No complaints of chill
218	novel clinical prediction rule
219	No blood drawn

Table S5. The corresponding mean weighted contribution and area under the receiver operating characteristic curves (AUROC) of 30 features selected by the wrapper algorithm around the random forest models in the training dataset. The feature candidates were ranked according to the AUROC.

Features	Mean weighted contribution	AUROC
IL-8*	9.34	0.83
SOFA total score	12.63	0.82
Albumin	5.23	0.80

D-dimer	6.74	0.77
Cortisol, ug/dL	3.04	0.74
Lactate	3.57	0.73
SOFA score -Respiratory	5.18	0.72
Red Blood Cell	4.07	0.71
IL-6*	4.99	0.71
FDP	4.50	0.69
SBC	3.88	0.69
Angiopoetin2	4.40	0.69
SOFA score -Coagulation	2.98	0.68
Platelet	6.37	0.68
Septic shock	2.76	0.67
Procalcitonin	4.19	0.66
Calcium, centered at 8.75 mg/dL	2.58	0.65
HCO3 centered at 25 mmol/L	3.46	0.64
Uric Acid	3.40	0.64
VCAM1*	3.78	0.64
pH	4.99	0.63
Pulse rate, centered at 100 BPM	3.05	0.61
Highest SOFA score cardiovascular	2.74	0.59
AaDO2	5.07	0.58
pCO2	3.23	0.58
SBE	3.79	0.56
ABE	3.97	0.56
FiO2	2.95	0.55
Total CO2	4.55	0.55
E-selectin *	3.86	0.54

*Values are normalized. ^δ The weighted contribution represents the importance and degree of influence of individual features in the dataset. Highly relevant features indicate a high probability of reaching the classification node and are given high weighted values, whereas irrelevant features weighted low values. Highest SOFA score cardiovascular: dopamine > 15 µg/kg/min OR epinephrine > 0.1 µg/kg/min OR norepinephrine > 0.1 µg/kg/min

Table S6. The AUROC performance of seven machine learning models when various features were selected by applying the SMOTE for both up-sampling down-sampling procedure.

Models	Dataset	Without SMOTE	With SMOTE(up-sampling)	With SMOTE(down-sampling)
Random Forest	Training	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
	Testing	0.96 (0.93-0.98)	0.92 (0.87-0.97)	0.94 (0.89-0.99)

Table S7. Sequential (sepsis-related) Organ Failure Assessment (SOFA) score.

Variable	Index	0	1	2	3	4
SOFA score						
SOFA_res	PaO ₂ /FiO ₂ , mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
SOFA_coag	Platelets, x10 ³ /uL	≥150	<150	<100	<50	<20
SOFA_liver	Bilirubin, mg/dL (umol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
SOFA_vas	MAP, Dop	MAP ≥ 70 mmHg	MAP < 70 mmHg	Dopamine <5 (ug/kg/min) or Dobutamine (ug/kg/min)	Dopamine 5.1-15 (ug/kg/min) or Epinephrine ≤ 0.1 or Norepinephrine ≤ 0.1	Dopamine >15 (ug/kg/min) or Epinephrine > 0.1 or Norepinephrine > 0.1
SOFA_renal	Creatinine, mg/dL (umol/L) Urine Output, mL/d	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440) <500	>5.0 (440) <200
SOFA_ner	Glasgow coma score	≥15	13-14	10-12	6-9	<6
Sepsis-3	SOFA score ≥ 2					
Septic shock	SOFA score ≥ 2 and Lactate >18 mmol/L					
ΔSOFA score	Difference between measured and baseline SOFA score					

Table S8. The summary descriptions of the selected eight algorithms.

Algorithms	Description
XGBoost	eXtreme Gradient Boosting (XGBoost) is a decision-tree-based algorithm that applies boosting methods to further improve performance on those misclassified observations.
CForest	Conditional random forest (CForest) is computationally more expensive and better than the Random forest package in terms of accuracy. CForest uses out-of-bag data to provide higher accuracy. It then uses a weighted average of the trees to get the final ensemble. CForest provides more reliable predictions by producing unbiased trees.
Random Forest	RF forms bagged decision tree models, which split on a subset of features on each split. By creating a multitude of decision trees to be trained on the training dataset, the predictive output value is the mode of the classes (classification) or mean prediction (regression) of the individual tree. By averaging away the variances of a number of trees, it helps to reduce the high variance derived from a single tree.
RANGER	RANdom forest GENeRator could build models quickly and find out optimal parameter values using parameter tuning. RANGER is used when dealing with high dimensional data and expects a memory-efficient fast implementation of RF.
ANN	Artificial Neural Networks are complex and flexible nonlinear systems. Hidden nodes link features with the outcomes, allowing nonlinear interactions among the features.
SVM	A support-vector machine constructs hyperplanes in a high- or infinite-dimensional space, which can be used for classification, regression, or other tasks like outliers detection. When the datasets to be discriminated are not linearly separable in a finite-dimensional space, SVM helps mapping into a much higher-dimensional space, making the separation and classification easier in that space.
Deep Learning	The deep learning method makes use of artificial neural networks, which constructs multiple layers to progressively extract higher-level features from the raw input. For supervised learning tasks, it translates the data into compact, intermediate representations akin to a principal component, and derives layered structures that remove redundant engineering features, thus can serve as validation of other machine learning algorithms.
Logistic regression	Logistic regression is similar to linear regression, which discovered the relationship between independent features (X) and dependent features (Y). The major difference is that the dependent feature (Y) is usually a continuous feature in linear regression but mainly a category feature in logistic regression.

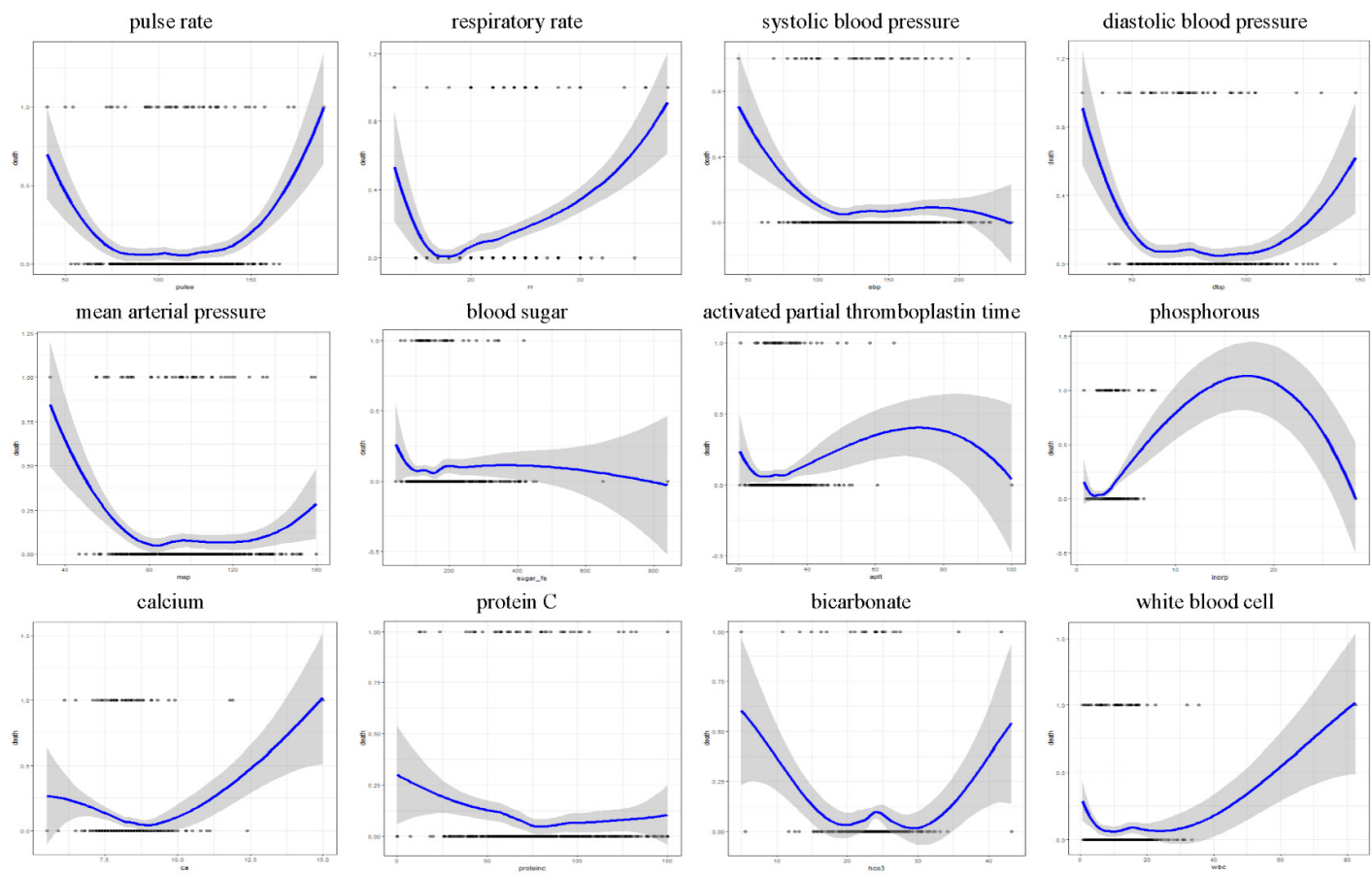


Figure S1. The U-shape distributions of 12 features.