

Supplemental material

Number of Supplemental Table: 6 Tables

Number of Supplemental Figure: 3 Figures

Table S1A. Assays and Manufactures for C-Reactive Protein Measurements

Assays	Manufactures
Latex agglutination	EIKEN CHEMICAL CO.,LTD. SEKISUI MEDICAL CO., LTD. NITTOBO MEDICAL CO.,LTD. FUJIFILM Wako Pure Chemical Corporation LSI Medience Corporation.
Latex turbidimetry	Shino-Test Corporation. LSI Medience Corporation. Roche Diagnostics K.K.

Table S1B. Assays and Manufactures D-dimer Measurements

Assays	Manufactures
Latex agglutination	LSI Medience Corporation. bioMérieux Japan Ltd. Roche Diagnostics K.K.
Latex turbidimetry	LSI Medience Corporation. bioMérieux Japan Ltd. Roche Diagnostics K.K. Sysmex Corporation. SEKISUI MEDICAL CO., LTD. KAINOS Laboratories, Inc. KYOKUTO PHARMACEUTICAL INDUSTRIAL CO., LTD.

Table S2. Univariate cox proportional hazard analysis for predictor of in-hospital mortality

Variables	HR	CI		p
Demographics and medical history				
Age	1.05	1.03	1.07	<0.001
Male	1.48	0.88	2.47	0.136
Japanese	21.10	0.06	7995.92	0.314
BMI	1.00	0.94	1.05	0.885
Comorbidities				
Hypertension	1.16	0.70	1.92	0.571
Diabetes mellitus	0.81	0.51	1.30	0.388
Dyslipidemia	0.73	0.45	1.18	0.198
Heart failure	1.59	0.85	2.94	0.145
Coronary artery disease	2.41	1.36	4.24	0.002
Myocardial infarction	1.58	0.72	3.46	0.252
CI/TIA	0.96	0.47	1.95	0.913
Chronic lung disease	3.11	1.63	5.91	0.001
CKD	1.73	0.93	3.21	0.084
Cancer	2.53	1.41	4.56	0.002
Symptoms				
Fever (> 38.0°C)	1.67	0.95	2.92	0.076
Cough	1.10	0.70	1.74	0.668
Pharyngitis	0.48	0.17	1.34	0.160
Rhinorrhea	0.86	0.26	2.84	0.801
Dyspnea	1.50	0.95	2.36	0.080
Arthritis	1.16	0.37	3.70	0.798
Headache	0.05	0.00	2.82	0.142
Olfactory dysfunction	0.05	0.00	4.02	0.176
Asymptom	0.56	0.18	1.79	0.330
Physical findings				
Max body temperature	1.38	1.04	1.84	0.027
Herat rate	1.02	1.00	1.03	0.017
Systolic BP	0.99	0.99	1.00	0.249
Respiratory rate	1.06	1.02	1.11	0.002
SpO2	0.95	0.92	0.98	0.003
Laboratory data at admission				
White blood cell	1.00	1.00	1.00	0.050
Lymphocyte	0.96	0.94	0.99	0.015

Neutrocyte	1.03	1.01	1.05	0.019
Eosinocyte	0.70	0.50	0.98	0.038
Hemoglobin	0.92	0.83	1.02	0.096
Platelet	0.95	0.91	0.98	0.001
Creatinin	1.14	1.04	1.24	0.003
eGFR	0.99	0.98	1.00	0.002
LDH	1.00	1.00	1.00	<0.001
HbA1c	0.80	0.60	1.07	0.137
CK	1.00	1.00	1.00	0.689
Serum Alb	0.51	0.36	0.73	<0.001
Specific biomarker at admission				
CRP	1.03	1.00	1.05	0.029
D-dimer	1.00	1.00	1.01	0.341
FDP	1.00	1.00	1.00	0.989
Ferritin	1.00	1.00	1.00	0.602
Procalcitonin	1.00	0.98	1.03	0.725
IL-6	1.00	0.99	1.01	0.944
KL-6	1.00	1.00	1.00	0.001
Both CRP and D-dimer were above Middle	3.46	1.72	6.96	<0.001

Data are shown as mean \pm standard deviation or median with interquartile range or percentage. Variables of laboratory

data were analyzed as continuous variables, except for cumulative variable of CRP and D-dimer. BMI: body mass

index, CI: cerebral infarction, TIA: transient ischemic attack, COPD: chronic obstructive pulmonary disease, CKD:

chronic kidney disease, BP: blood pressure, eGFR: estimated glomerular filtration rate, LDH: lactic acid

dehydrogenase, HbA1c: hemoglobin A1c, CK: creatine kinase, Alb: albumin, CRP: C-reactive protein, FDP: fibrin

degradation products, KL-6: Krebs von den Lungen-6 antigen.

Table S3. Multivariate cox proportional hazard analysis for predictor of in-hospital mortality

Variables	HR	CI	p	
Demographics and medical history				
Age	1.07	1.023	1.111	0.003
Coronary artery disease	3.39	1.358	8.445	0.009
COPD	1.18	0.353	3.917	0.793
CKD	1.92	0.592	6.195	0.278
Cancer	0.66	0.213	2.042	0.470
Dyspnea	0.85	0.360	1.989	0.702
Max body temperature	1.56	0.980	2.472	0.061
Heart rate	1.02	0.993	1.039	0.183
SpO2	0.96	0.899	1.034	0.303
White blood cell	1.00	1.000	1.000	0.944
Hemoglobin	1.04	0.829	1.299	0.748
Platelet	0.92	0.857	0.992	0.030
LDH	1.00	0.998	1.004	0.521
Serum Alb	0.83	0.315	2.189	0.706
KL-6	1.00	1.000	1.002	0.181
Both CRP and D-dimer were above Middle	3.88	1.185	12.728	0.025

The Cox proportional hazard model predicting the odds of in-hospital mortality, adjusted for demographics and clinical comorbidities. Variables of laboratory data were analyzed as continuous variables, except for cumulative variable of CRP and D-dimer. Covariates included in the multivariable were selected based on univariate analyses.

HR: hazard ratio, CI: confidence interval, BMI: body mass index, COPD: chronic obstructive pulmonary disease,

CKD: chronic kidney disease, LDH: lactic acid dehydrogenase, Alb: albumin, KL-6: Krebs von den Lungen-6 antigen,

CRP: C-reactive protein.

Table S4. Biomarker levels at each timing of admission, peak, and final examination

	In-hospital death (<i>n</i> =108)	<i>n</i>	Non in-hospital death (<i>n</i> =585)	<i>n</i>	<i>P</i> Value
CRP, mg/L					
At admission	107.2 (56.9 – 168.9)	108	49.6 (13.4 – 104.5)	559	<0.001
Peak	247.6 (153.3 – 326.7)	104	816.2 (301.5 – 1524.3)	544	<0.001
Final	156.0 (748.5 – 2374.5)	92	4.7 (1.4 – 17.5)	484	<0.001
D-dimer, mg/L					
At admission	2.15 (1.32 - 5.08)	76	1.30 (0.70 - 2.60)	385	<0.001
Peak	14.1 (3.7 - 51.9)	82	2.40 (1.00 - 7.12)	403	<0.001
Final	14.2 (5.93 - 36.1)	58	1.90 (1.01 - 4.00)	239	<0.001

CRP: C-reactive protein.

Table S5. The increment of biomarker values between baseline and peak

	In-hospital death (<i>n</i> =108)	<i>n</i>	Non in-hospital death (<i>n</i> =585)	<i>n</i>	<i>P</i> Value
CRP, mg/L	117.1 (15.1 – 209.2)	104	0.15 (0.00 – 52.3)	544	<0.001
D-dimer, mg/L	6.05 (0.00 - 31.1)	74	0.00 (0.00 - 2.69)	376	<0.001
FDP, µg/mL	1.3 (0.00 - 50.0)	50	0.00 (0.00 - 2.90)	158	0.004
Ferritin, ng/mL	29.5 (0.00 - 750.0)	40	0.00 (0.00 - 15.0)	271	0.001
Procalcitonin, ng/mL	0.22 (0.00 - 2.14)	52	0.00 (0.00 - 0.00)	205	<0.001
KL6, U/mL	0.00 (0.00 - 269.0)	46	0.00 (0.00 - 0.00)	240	0.002

CRP: C-reactive protein, FDP: fibrin degradation products, KL-6: Krebs von den Lungen-6 antigen.

Table S6. Timing of peak value of each biomarker (Days from discharge)

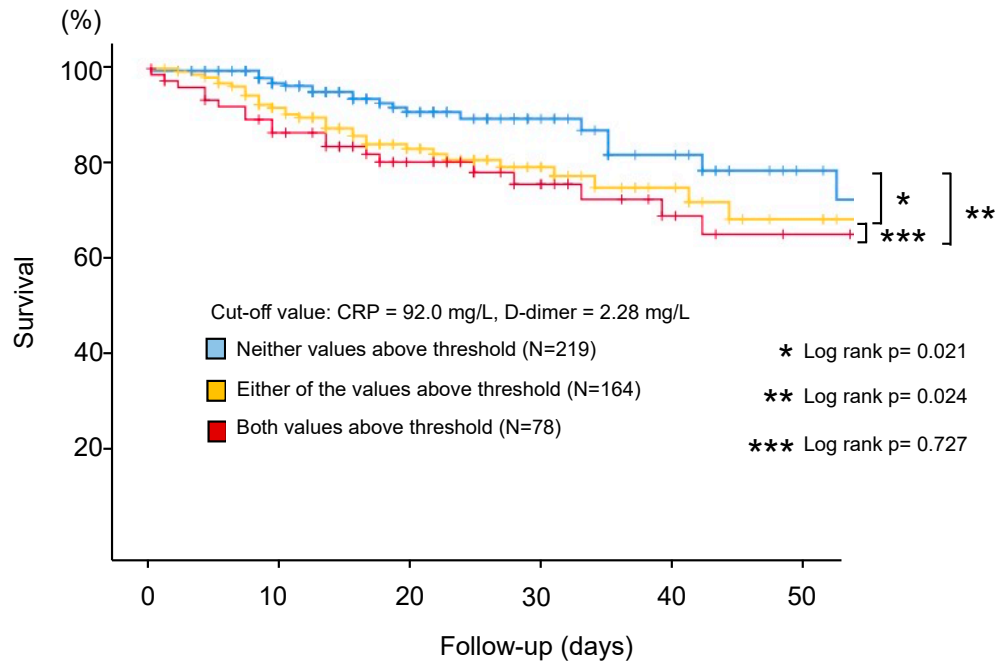
	In-hospital death (<i>n</i> =108)	<i>n</i>	Non in-hospital death (<i>n</i> =585)	<i>n</i>	<i>P</i> Value
CRP	4.5 (0.25 - 14.0)	104	15.0 (9.0 - 24.0)	546	<0.001
D-dimer	5.0 (1.0 - 13.0)	82	13.5 (8.0 - 23.8)	404	<0.001
FDP	8.0 (1.0 - 22.0)	59	16.0 (9.0 - 28.0)	179	0.001
Ferritin	7.0 (1.0 - 19.0)	49	15.0 (9.8 - 25.3)	302	<0.001
Procalcitonin	8.0 (2.0 - 23.0)	55	17.0 (11.0 - 24.0)	222	0.001
KL6	8.5 (5.3 - 18.8)	48	14.0 (8.0 - 25.0)	267	0.012

CRP: C-reactive protein, FDP: fibrin degradation products, KL-6: Krebs von den Lungen-6 antigen.

Supplemental Figure

Figure S1

(A)



(B)

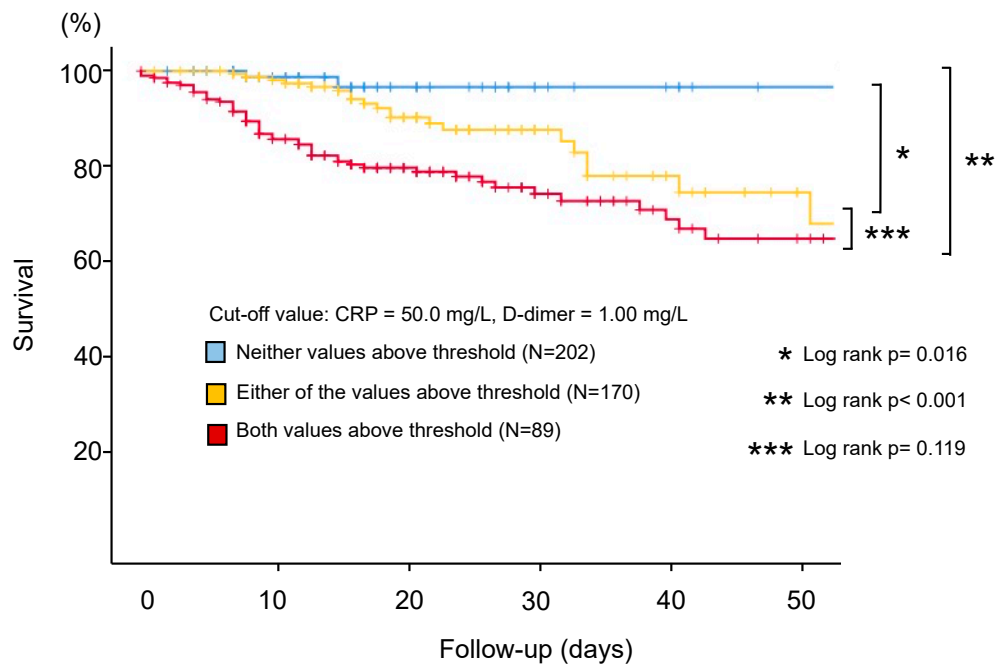


Figure S2

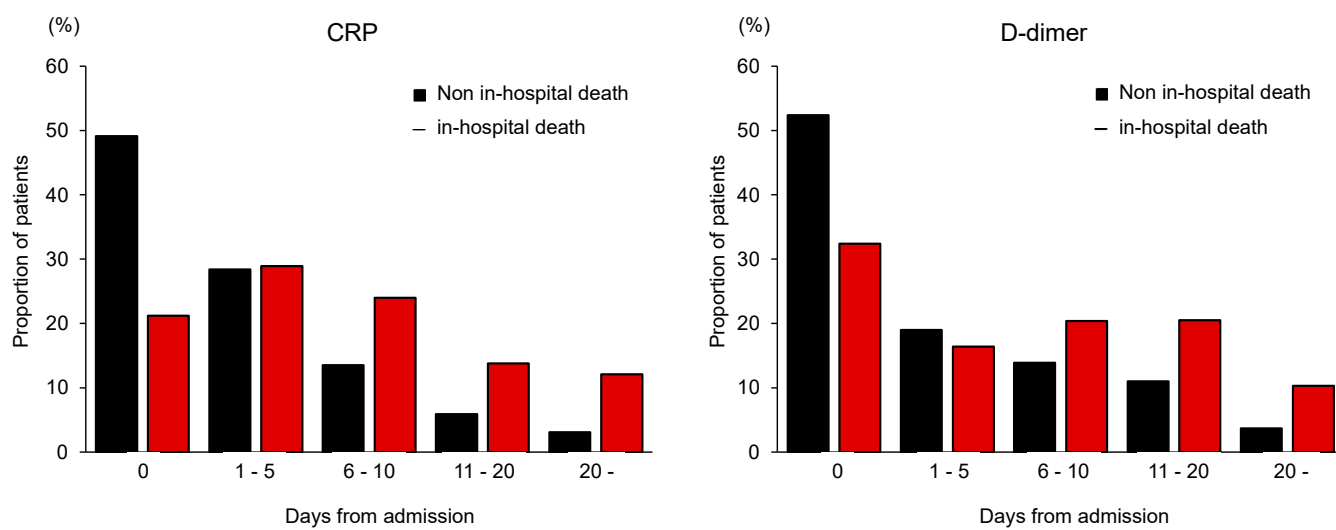
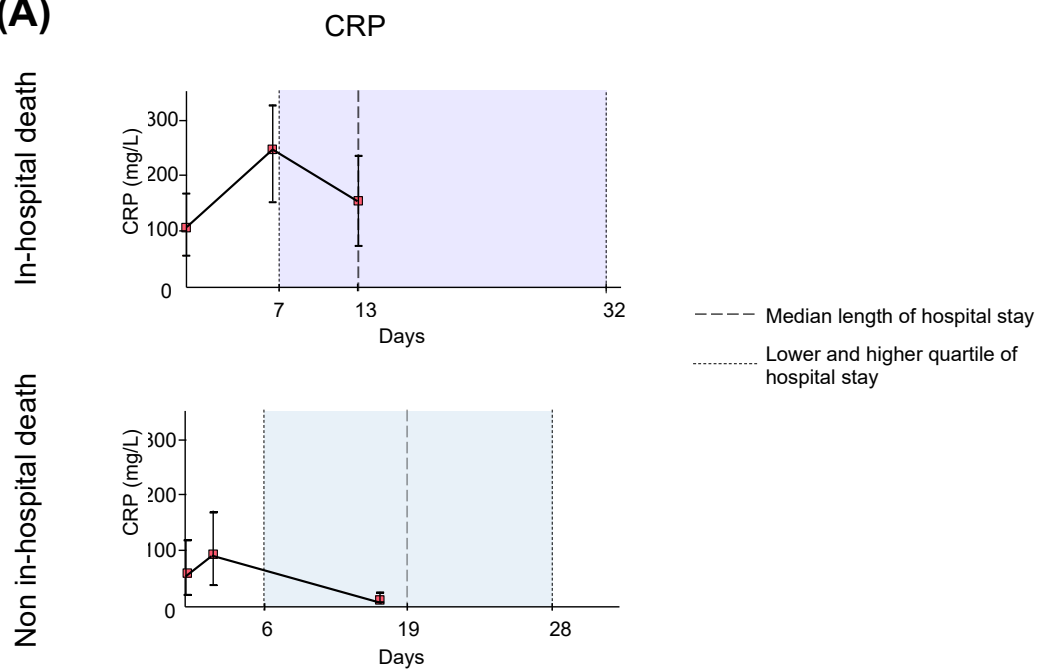
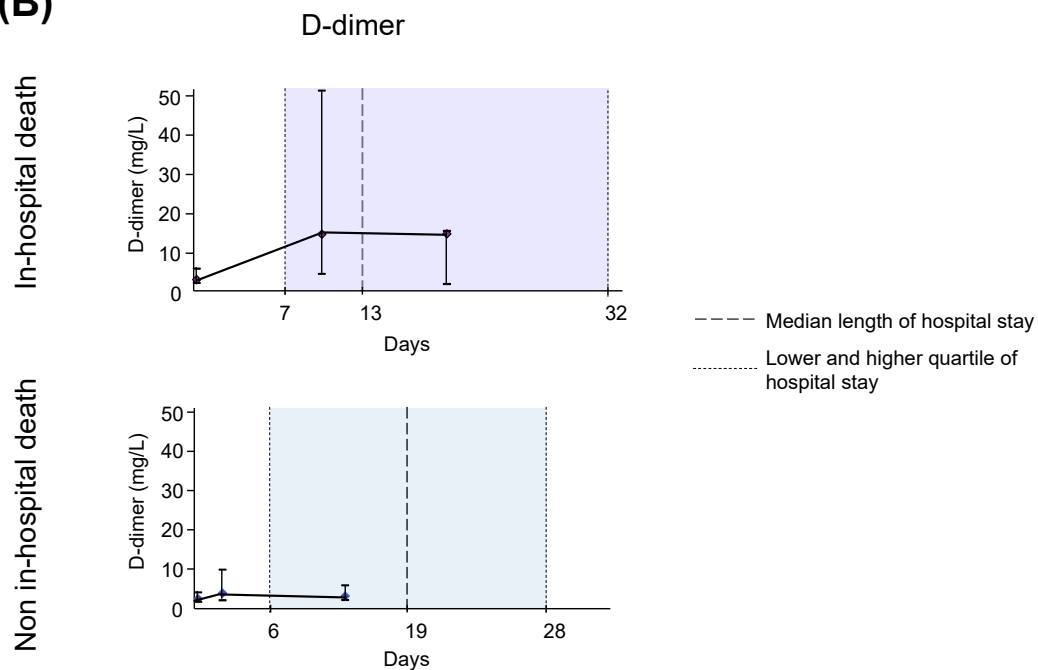


Figure S3

(A)

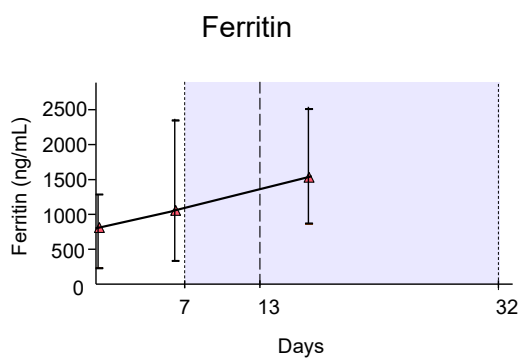


(B)

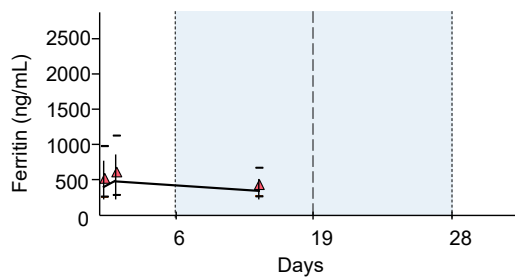


(C)

In-hospital death

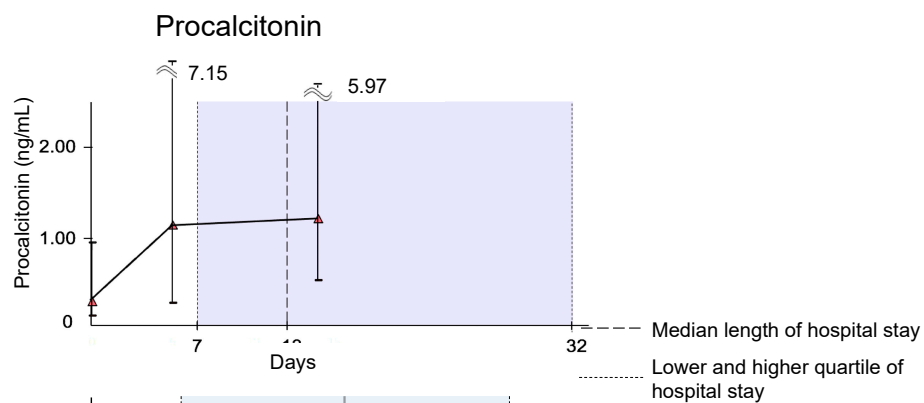


Non in-hospital death

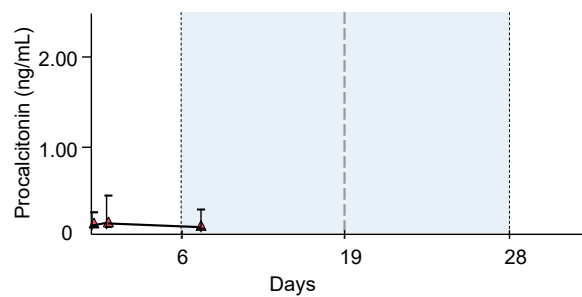


(D)

In-hospital death

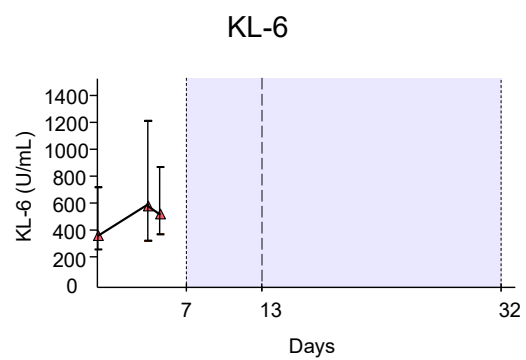


Non in-hospital death



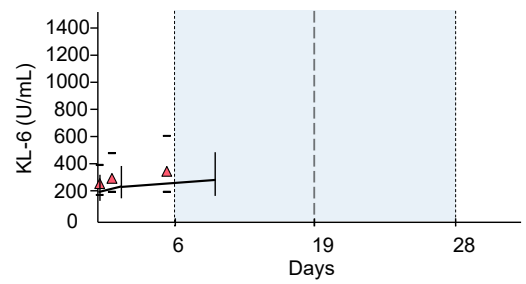
(E)

In-hospital death



--- Median length of hospital stay
..... Lower and higher quartile of hospital stay

Non in-hospital death



Supplemental Figure Legend

Figure S1: Sensitivity analysis with additional threshold values to evaluate the incidence of in-hospital death. Threshold values were: (A) CRP, 92.0 mg/L; D-dimer, 2.28 mg/L, and (B) CRP, 50.0 mg/L; D-dimer, 1.00 mg/L. CRP: C-reactive protein. CRP: C-reactive protein.

Figure S2: Proportion of patients whose peak CRP and D-dimer values were recorded at the indicated time points (days from admission). CRP: C-reactive protein.

Figure S3: Trajectories of other biomarkers over time among survival and in-hospital deaths. (A) CRP, (B) D-dimer, (C) ferritin, (D) procalcitonin, and (E) KL-6. CRP: C-reactive protein.