

Supplemental Materials

Table S1. Comparison of clinical characteristics among the phenotypes of patients in the retrospective cohort.

Characteristic	Overall	α	β	γ	δ	p
n	2149	81	1488	69	511	
Age (mean (SD))	59.39 (17.58)	59.56 (16.18)	59.23 (17.58)	54.70 (20.16)	60.46 (17.36)	0.073
Sex (Male, %)	1310 (61.0)	42 (51.9)	929 (62.4)	40 (58.0)	299 (58.5)	0.126
APACHE-II (mean (SD))	19.66 (7.67)	23.03 (8.00)	19.10 (7.48)	17.08 (7.01)	21.05 (7.89)	<0.001
SOFA (mean (SD))	9.06 (4.01)	11.11 (3.79)	8.67 (3.98)	8.22 (3.22)	9.98 (3.99)	<0.001
LY-D1 (x10⁹/L, mean (SD))	0.91 (0.53)	1.44 (0.52)	1.06 (0.50)	0.51 (0.27)	0.45 (0.22)	<0.001
LY-D2 (x10⁹/L, mean (SD))	0.97 (0.53)	0.99 (0.44)	1.15 (0.50)	0.99 (0.49)	0.43 (0.18)	<0.001
LY-D3 (x10⁹/L, mean (SD))	0.96 (0.53)	0.61 (0.24)	1.15 (0.46)	1.44 (0.63)	0.41 (0.16)	<0.001
LY-D4 (x10⁹/L, mean (SD))	0.95 (0.52)	0.45 (0.18)	1.13 (0.44)	1.78 (0.64)	0.42 (0.16)	<0.001
HR (bpm, mean (SD))	101.94 (21.69)	105.80 (24.75)	101.43 (21.38)	103.26 (22.18)	102.64 (21.99)	0.245
T (°C, mean (SD))	36.85 (1.08)	37.19 (1.29)	36.87 (1.08)	37.00 (1.06)	36.71 (1.04)	<0.001
RR (/min, mean (SD))	20.94 (6.72)	22.14 (7.26)	20.75 (6.49)	21.19 (6.69)	21.27 (7.27)	0.171
OI (mmHg, median [IQR])	215.00 [153.55, 293.30]	205.70 [149.50, 285.48]	219.55 [159.35, 300.00]	227.50 [184.55, 294.35]	204.25 [135.22, 280.53]	<0.001
Lactate (mmol/L, median [IQR])	2.10 [1.30, 3.80]	3.30 [1.80, 6.32]	2.00 [1.30, 3.50]	2.00 [1.37, 3.25]	2.40 [1.40, 4.00]	<0.001
Length of ICU stay (days, median [IQR])	7.00 [3.90, 13.80]	7.80 [4.30, 13.80]	7.10 [3.90, 13.90]	5.50 [3.00, 8.90]	7.00 [3.90, 13.90]	0.011
Duration of vasopressor (hours, median [IQR])	106.22 [50.00, 220.00]	101.50 [58.42, 241.04]	106.10 [51.00, 214.50]	75.06 [39.19, 131.81]	108.50 [49.30, 242.00]	0.351
Duration of mechanical ventilation (hours, median [IQR])	111.10 [47.75, 239.17]	156.67 [63.07, 301.25]	109.28 [42.00, 221.30]	64.67 [35.18, 127.57]	123.00 [55.00, 276.25]	0.001
Infection source (%)						
CNS	18 (0.8)	0 (0.0)	14 (0.9)	1 (1.4)	3 (0.6)	<0.001

Characteristic	Overall	α	β	γ	δ	p
SST	79 (3.7)	0 (0.0)	63 (4.2)	6 (8.7)	10 (2.0)	
Valves	84 (3.9)	6 (7.4)	68 (4.6)	5 (7.2)	5 (1.0)	
Lung	1220 (56.8)	50 (61.7)	835 (56.1)	31 (44.9)	304 (59.5)	
Intra-abdominal	502 (23.4)	18 (22.2)	328 (22.0)	15 (21.7)	141 (27.6)	
UTI	10 (0.5)	0 (0.0)	7 (0.5)	3 (4.3)	0 (0.0)	
Others	140 (6.5)	5 (6.2)	104 (7.0)	5 (7.2)	26 (5.1)	
Pleural	53 (2.5)	1 (1.2)	39 (2.6)	1 (1.4)	12 (2.3)	
Bloodstream	42 (2.0)	1 (1.2)	30 (2.0)	2 (2.9)	9 (1.8)	
Mediastinum	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	
28-Day Mortality (%)	351 (16.3)	21 (25.9)	209 (14.0)	5 (7.2)	116 (22.7)	<0.001

Abbreviations: SD, standard deviation, IQR, interquartile range, APACHE-II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; HR, heart rate; T, temperature; RR, respiratory rate; OI, oxygenation index; LY, lymphocyte count; D1–D4, 1–4 days after intensive care unit admission. CNS, central nervous system; SST, skin, and soft tissue; UTI, urinary tract infection.

Table S2. Comparison of clinical characteristics among the phenotypes of patients in the external validation cohort.

Characteristic	Overall	α	β	γ	δ	p
n	2388	91	1043	780	474	
Age (mean (SD))	64.76 (16.21)	62.52 (17.34)	65.89 (15.83)	63.05 (17.47)	65.50 (14.29)	0.001
Sex (Male, %)	1059 (44.3)	33 (36.3)	438 (42.0)	398 (51.0)	190 (40.1)	<0.001
SAPS-II (mean (SD))	43.75 (14.66)	45.27 (14.82)	44.28 (14.23)	41.09 (14.92)	46.65 (14.45)	<0.001
SOFA (mean (SD))	4.20 (2.36)	4.01 (1.83)	4.14 (2.36)	4.03 (2.30)	4.62 (2.52)	<0.001
LY-D1 (x10 ⁹ /L, mean (SD))	1.12 (0.90)	2.49 (1.08)	0.83 (0.50)	1.70 (1.00)	0.51 (0.38)	<0.001
LY-D2 (x10 ⁹ /L, mean (SD))	1.04 (0.87)	1.67 (1.29)	0.79 (0.43)	1.80 (0.93)	0.34 (0.23)	<0.001
LY-D3 (x10 ⁹ /L, mean (SD))	1.00 (0.81)	0.88 (0.71)	0.79 (0.35)	1.90 (0.83)	0.30 (0.20)	<0.001
LY-D4 (x10 ⁹ /L, mean (SD))	1.05 (0.75)	0.47 (0.27)	0.91 (0.34)	1.82 (0.75)	0.32 (0.17)	<0.001
HR (bpm, mean (SD))	91.00 (17.48)	93.53 (17.32)	90.60 (17.34)	90.14 (17.07)	92.83 (18.33)	0.023
T (°C, mean (SD))	36.99 (0.61)	37.01 (0.58)	36.99 (0.63)	36.99 (0.58)	36.98 (0.61)	0.971
RR (/min, mean (SD))	20.98 (4.31)	21.07 (4.18)	21.00 (4.35)	20.97 (4.34)	20.93 (4.19)	0.991
OI (mmHg, median [IQR])	175.00 [110.00, 260.36]	200.00 [116.00, 301.00]	172.00 [108.75, 262.38]	174.50 [115.00, 252.38]	166.67 [100.00, 257.50]	0.462
Lactate (median [IQR])	2.30 [1.40, 4.50]	2.65 [1.72, 6.05]	2.20 [1.40, 4.30]	2.30 [1.50, 4.40]	2.70 [1.50, 4.90]	0.048
Length of ICU stay (days, median [IQR])	5.22 [3.17, 9.88]	5.11 [3.33, 8.62]	5.19 [3.15, 9.80]	5.18 [3.23, 9.74]	5.73 [3.03, 10.69]	0.810
Duration of vasopressor (hours, median [IQR])	65.00 [29.75, 149.25]	68.00 [37.00, 142.00]	67.00 [30.00, 152.00]	59.00 [30.00, 131.00]	76.50 [27.00, 163.50]	0.552
Duration of mechanical ventilation (hours, median [IQR])	68.50 [34.00, 146.25]	68.00 [35.00, 133.00]	74.00 [34.00, 151.00]	61.00 [30.00, 132.00]	85.00 [40.50, 160.00]	0.007
28-Day Mortality (%)	613 (25.7)	35 (38.5)	263 (25.2)	165 (21.2)	150 (31.6)	<0.001

Abbreviations: SD, standard deviation, IQR, interquartile range, SAPS II, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; HR, heart rate; T, temperature; RR, respiratory rate; OI, oxygenation index; LY, lymphocyte count; D1–D4, 1–4 days after intensive care unit admission.

Table S3. Comparison of clinical characteristics among the phenotypes of patients with sepsis in the prospective cohort.

Characteristic	Overall	α	β	γ	δ	p
n	1056	241	535	225	55	
Age (mean (SD))	60.0 (16.6)	63.8 (15.1)	57.1 (16.8)	62.5 (16.3)	62.6 (17.6)	<0.001
Sex (Male, %)	688 (65.2)	156 (64.7)	358 (66.9)	144 (64.0)	30 (54.5)	0.307
APACHE-II (mean (SD))	19.8 (7.5)	21.3 (7.5)	18.6 (6.9)	20.2 (7.8)	24.4 (7.6)	<0.001
SOFA (mean (SD))	6.9 (3.0)	7.0 (2.8)	7.0 (2.9)	6.6 (3.3)	6.7 (3.6)	0.353
HR (mean (SD))	102.1 (20.6)	102.8 (21.0)	100.7 (19.8)	103.4 (21.3)	107.5 (21.8)	0.062
T (mean (SD))	36.7 (1.0)	36.6 (1.0)	36.7 (0.9)	36.6 (1.0)	36.8 (1.0)	0.729
RR (mean (SD))	16.1 (7.7)	15.9 (6.7)	16.1 (8.5)	15.6 (6.6)	18.8 (7.9)	0.079
OI (mmHg, median [IQR])	211.9 [151.3, 281.2]	202.4 [144.6, 266.0]	219.3 [156.2, 288.9]	209.0 [152.5, 282.9]	179.5 [130.9, 262.9]	0.040
Lactate (mmol/L, median [IQR])	2.6 [1.7, 5.0]	3.0 [1.8, 6.0]	2.5 [1.6, 5.0]	2.4 [1.6, 4.1]	2.7 [1.8, 5.2]	0.020
BLC (mean (SD))	143.6 (150.1)	102.0 (88.5)	197.1 (180.2)	89.1 (72.3)	30.6 (31.3)	<0.001
TLC (mean (SD))	610.7 (394.0)	416.2 (199.4)	844.9 (389.2)	370.5 (203.5)	172.3 (197.8)	<0.001
CD4+TLC (mean (SD))	362.4 (246.4)	251.1 (140.0)	498.4 (251.0)	224.3 (133.2)	95.5 (110.5)	<0.001
CD8+TLC (mean (SD))	217.0 (182.9)	146.6 (109.8)	301.0 (202.7)	129.8 (97.8)	67.4 (88.6)	<0.001
CD4/CD8 (mean (SD))	2.3 (2.1)	2.4 (2.1)	2.2 (1.7)	2.5 (2.4)	2.4 (3.9)	0.426
NK-LC (mean (SD))	89.5 (89.3)	70.3 (71.4)	115.9 (102.1)	62.3 (56.7)	28.8 (38.3)	<0.001
Length of ICU stay (days, median [IQR])	7.2 [4.8, 16.8]	9.6 [4.8, 19.2]	7.2 [4.8, 14.4]	7.2 [2.4, 14.4]	9.6 [7.2, 18.0]	<0.001
Duration of vasopressor (hours, median [IQR])	112.3 [51.0, 261.6]	139.8 [64.9, 337.7]	105.0 [46.7, 237.1]	99.0 [45.2, 240.2]	165.9 [85.0, 333.1]	<0.001
Duration of mechanical ventilation (hours, median [IQR])	118.2 [55.9, 277.5]	148.2 [64.7, 364.4]	103.9 [48.0, 238.5]	113.8 [39.7, 266.1]	218.9 [130.8, 356.7]	<0.001
Infection source (%)						
CNS	2 (0.2)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0.008
SST	26 (2.5)	3 (1.2)	13 (2.4)	10 (4.4)	0 (0.0)	

Characteristic	Overall	α	β	γ	δ	p
Valves	57 (5.4)	10 (4.1)	40 (7.5)	6 (2.7)	1 (1.8)	
Lung	753 (71.3)	181 (75.1)	375 (70.1)	147 (65.3)	50 (90.9)	
Intra-abdominal	167 (15.8)	35 (14.5)	77 (14.4)	52 (23.1)	3 (5.5)	
UTI	3 (0.3)	1 (0.4)	1 (0.2)	0 (0.0)	1 (1.8)	
Others	13 (1.2)	3 (1.2)	8 (1.5)	2 (0.9)	0 (0.0)	
Pleural	19 (1.8)	5 (2.1)	11 (2.1)	3 (1.3)	0 (0.0)	
Bloodstream	15 (1.4)	3 (1.2)	8 (1.5)	4 (1.8)	0 (0.0)	
Mediastinum	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	
28-Day Mortality (%)	173 (16.4)	55 (22.8)	62 (11.6)	35 (15.6)	21 (38.2)	<0.001

Abbreviations: SD, standard deviation, IQR, interquartile range, APACHE-II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; HR, heart rate; T, temperature; RR, respiratory rate; OI, oxygenation index; BLC, B-lymphocyte count; TLC, T-lymphocyte count; NK, natural killer; CNS, central nervous system; SST, skin, and soft tissue; UTI, urinary tract infection.

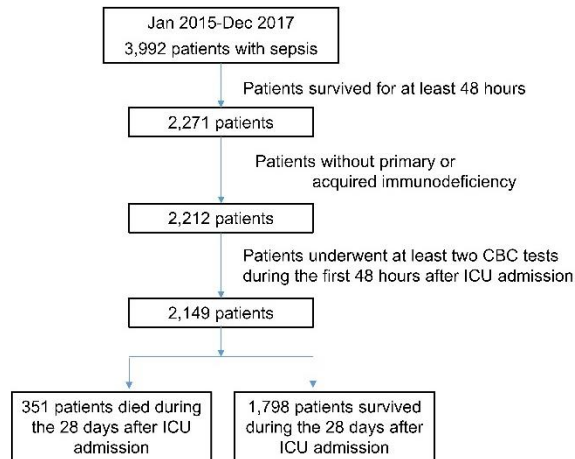
Table S4. Clinical characteristics among patients in the prospective cohort categorized by 28-day mortality.

Characteristic	Overall	No	Yes	<i>p</i>
n	1056	883	173	
Age (mean (SD))	60.0 (16.6)	59.4 (16.6)	63.5 (16.2)	0.003
Sex (Male, %)	688 (65.2)	579 (65.6)	109 (63.0)	0.575
APA (mean (SD))	19.8 (7.5)	19.1 (7.0)	23.9 (8.5)	<0.001
SOFA (mean (SD))	6.9 (3.0)	6.9 (3.0)	6.8 (2.9)	0.772
HR (mean (SD))	102.1 (20.6)	101.1 (19.8)	107.3 (23.5)	<0.001
T (mean (SD))	36.7 (1.0)	36.6 (0.9)	36.9 (1.0)	<0.001
RR (mean (SD))	16.1 (7.7)	15.8 (7.8)	17.1 (7.4)	0.054
PFO₂ (mmHg, median [IQR])	211.9 [151.3, 281.2]	214.0 [156.2, 284.9]	181.7 [138.2, 265.4]	0.002
Lactate (mmol/L, median [IQR])	2.6 [1.7, 5.0]	2.6 [1.6, 5.0]	2.5 [1.8, 4.6]	0.800
BLC (mean (SD))	143.6 (150.1)	148.8 (154.9)	117.0 (119.1)	0.012
TLC (mean (SD))	610.7 (394.0)	630.9 (389.2)	506.0 (403.4)	<0.001
CD4+TLC (mean (SD))	362.4 (246.4)	371.7 (240.2)	314.3 (272.2)	0.005
CD8+TLC (mean (SD))	217.0 (182.9)	226.0 (183.3)	170.8 (174.0)	<0.001
CD4/CD8 (mean (SD))	2.3 (2.1)	2.3 (2.0)	2.6 (2.5)	0.037
NK-LC (mean (SD))	89.5 (89.3)	94.5 (90.0)	64.0 (81.4)	<0.001
Length of ICU stay (days, median [IQR])	0.3 [0.2, 0.7]	0.3 [0.2, 0.6]	0.5 [0.3, 0.9]	<0.001
Duration of vasopressor (hours, median [IQR])	112.3 [51.0, 261.6]	94.0 [45.2, 217.5]	261.7 [107.6, 468.7]	<0.001
Duration of mechanical ventilation (hours, median [IQR])	118.2 [55.9, 277.5]	104.5 [41.5, 230.2]	275.6 [136.1, 499.2]	<0.001
Infection source (%)				
CNS	2 (0.2)	2 (0.2)	0 (0.0)	<0.001
SST	26 (2.5)	23 (2.6)	3 (1.7)	
Valves	57 (5.4)	55 (6.2)	2 (1.2)	
Lung	753 (71.3)	599 (67.8)	154 (89.0)	
Intra-abdominal	167 (15.8)	155 (17.6)	12 (6.9)	
UTI	3 (0.3)	2 (0.2)	1 (0.6)	
Others	13 (1.2)	13 (1.5)	0 (0.0)	
Pleural	19 (1.8)	19 (2.2)	0 (0.0)	

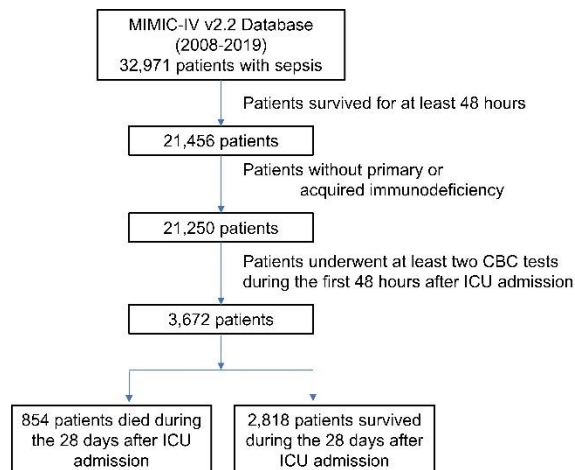
Characteristic	Overall	No	Yes	<i>p</i>
Bloodstream	15 (1.4)	14 (1.6)	1 (0.6)	
Mediastinum	1 (0.1)	1 (0.1)	0 (0.0)	
72-hour Lymphocyte trajectory phenotype (%)				
α	241 (22.8)	186 (21.1)	55 (31.8)	<0.001
β	535 (50.7)	473 (53.6)	62 (35.8)	
γ	225 (21.3)	190 (21.5)	35 (20.2)	
δ	55 (5.2)	34 (3.9)	21 (12.1)	

Abbreviations: APACHE-II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; HR, heart rate; T, temperature; RR, respiratory rate; OI, oxygenation index; BLC, B-lymphocyte count; TLC, T-lymphocyte count; NK, natural killer; CNS, central nervous system; SST, skin and soft tissue; UTI, urinary tract infection.

A.



B.



C.

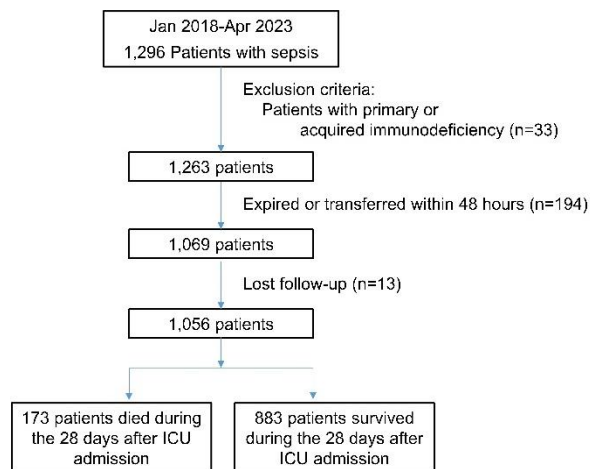
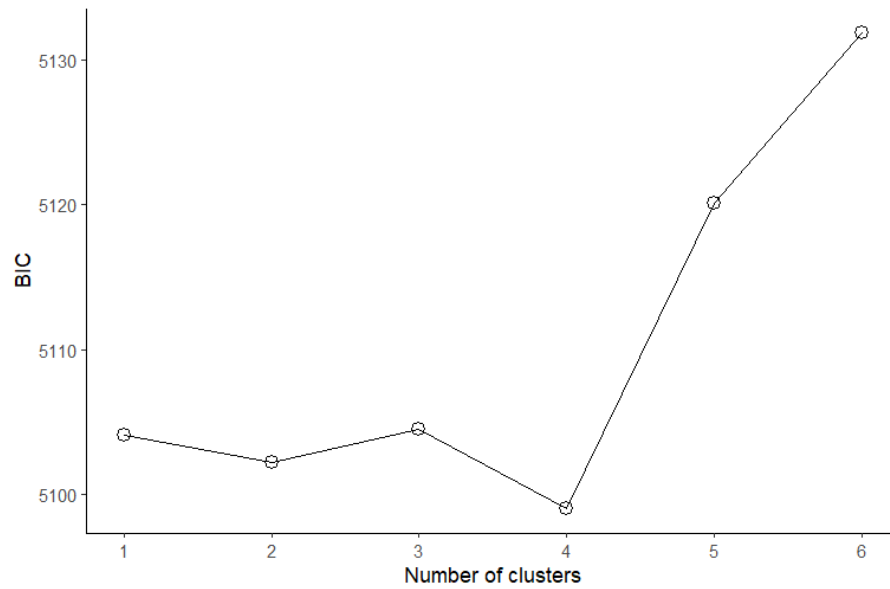
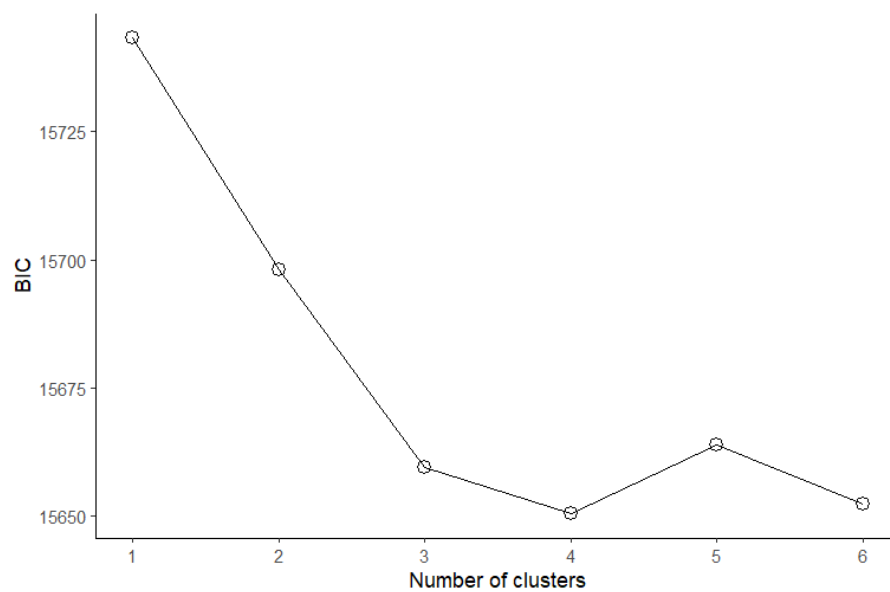


Figure S1. Flowcharts of the study protocol. A. Retrospective (PUMCH) cohort. B.

External validation (MIMIC-IV) cohort. C. Prospective (PUMCH) cohort. Abbreviations: MIMIC, Medical Information Mart for Intensive Care; PUMCH, Peking Union Medical College Hospital. ICU, Intensive Care Unit. CBC, Complete Blood Count.

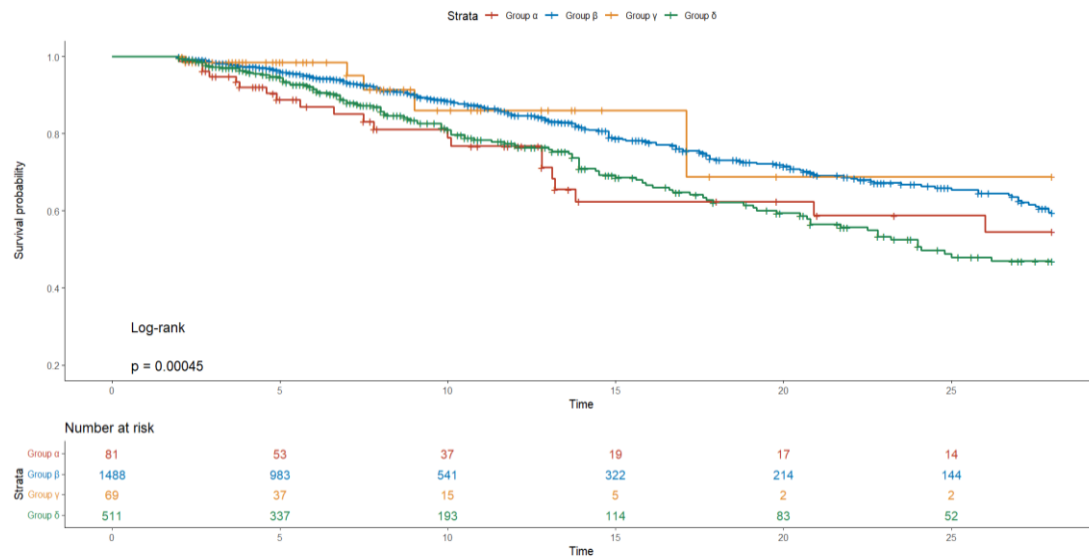


A.

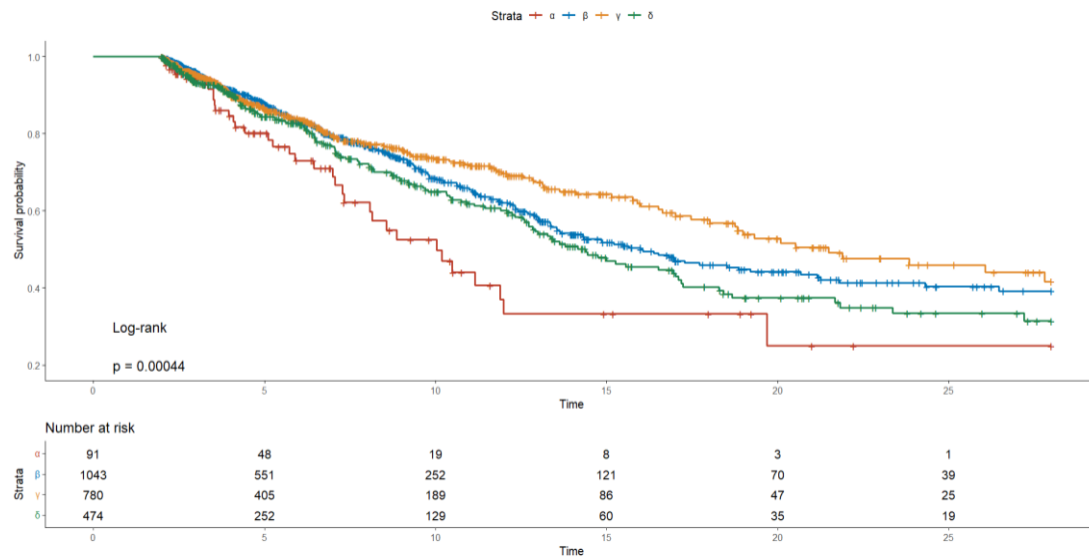


B.

Figure S2. Bayesian information criterion scores for various cluster number. The x-axis represents the number of clusters, while the y-axis represents the Bayesian information criterion value. A. Retrospective PUMCH cohort. B. External validation MIMIC-IV cohort. Abbreviations: MIMIC, Medical Information Mart for Intensive Care; PUMCH, Peking Union Medical College Hospital. BIC, Bayesian information criterion.

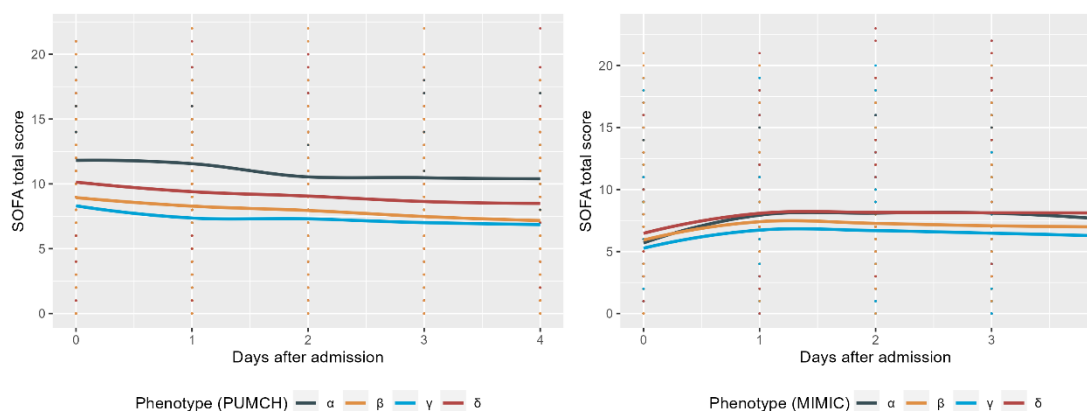


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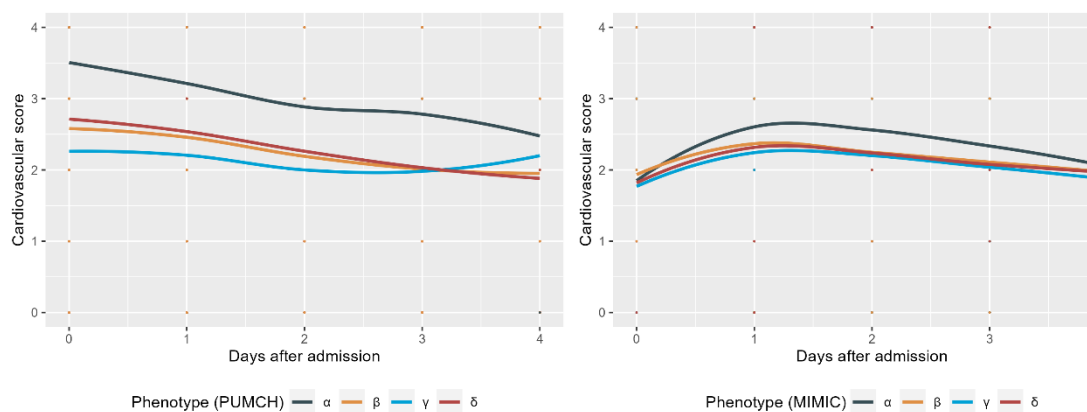


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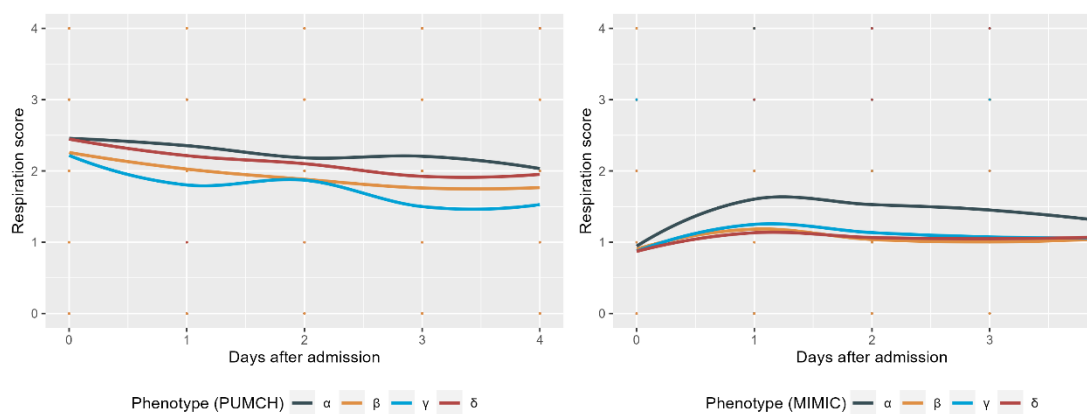
Figure S3. Survival curves of 28-day mortality by phenotype. A. Retrospective (PUMCH) cohort. B, External validation (MIMIC) cohort. The P value (log-rank test) for the comparison among the survival curves of the four phenotypes at ICU discharge is shown. Abbreviations: MIMIC, Medical Information Mart for Intensive Care; PUMCH, Peking Union Medical College Hospital. ICU, Intensive Care Unit.



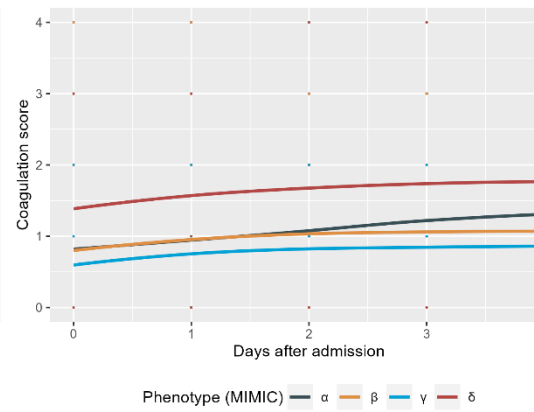
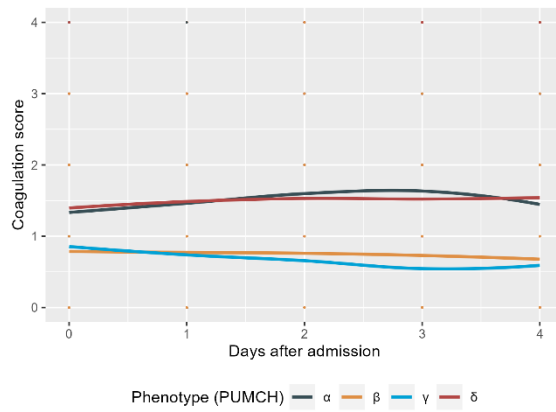
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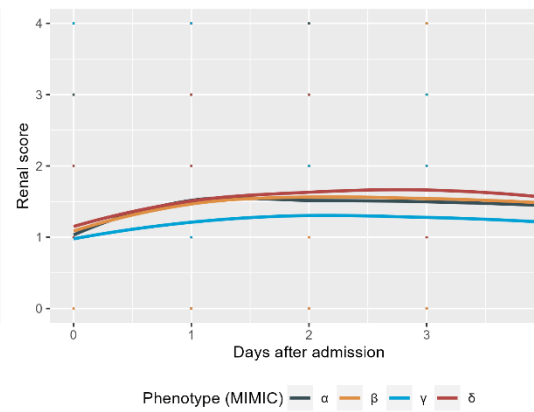
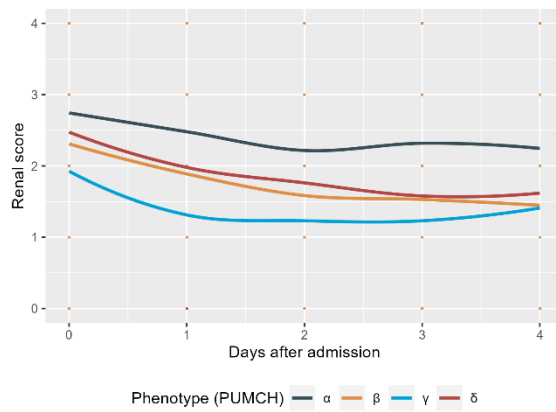
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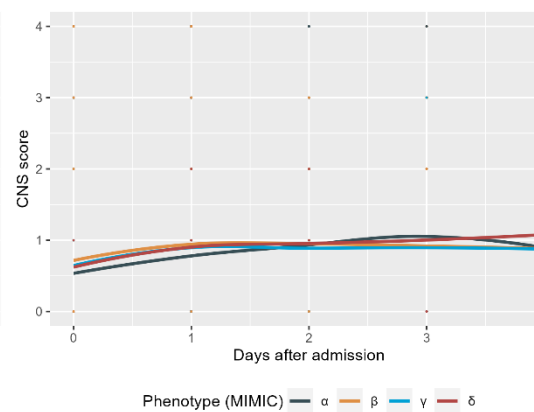
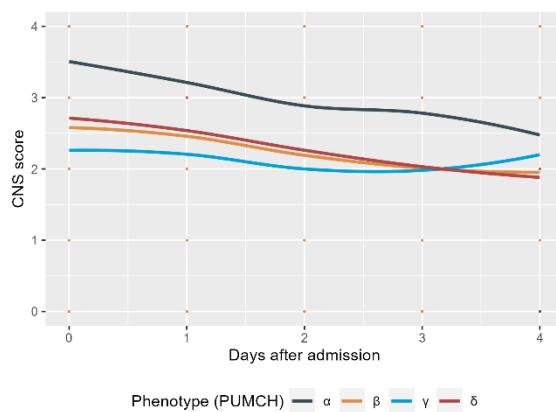
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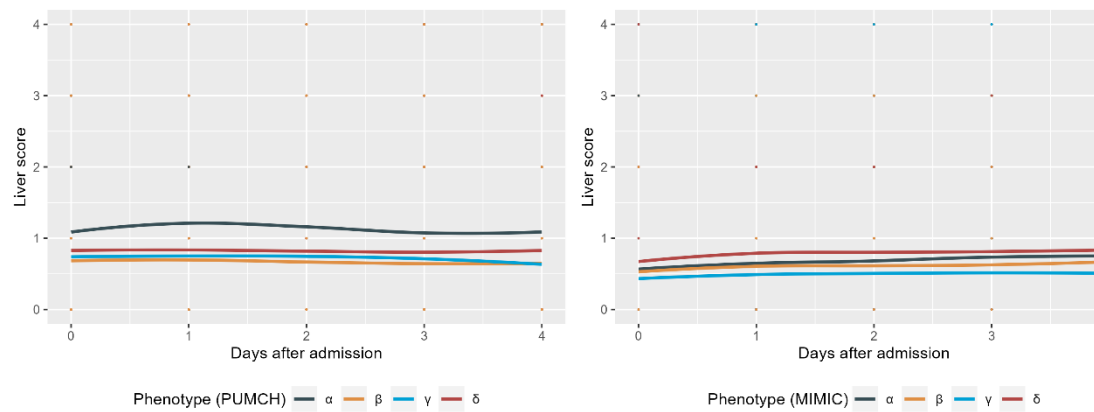
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E



F



G

Figure S4. Longitudinal trajectory of the SOFA sub-score for each lymphocyte trajectory phenotype in the retrospective and external validation cohorts. The total SOFA score trajectory of each of the PUMCH cohort (A, left) and MIMIC-IV cohort (A, right) is illustrated in A, while the SOFA sub-score trajectory is represented in B–G. The organ systems are indicated on the y-axis. Abbreviations: MIMIC, Medical Information Mart for Intensive Care; PUMCH, Peking Union Medical College Hospital. SOFA, Sequential Organ Failure Assessment.

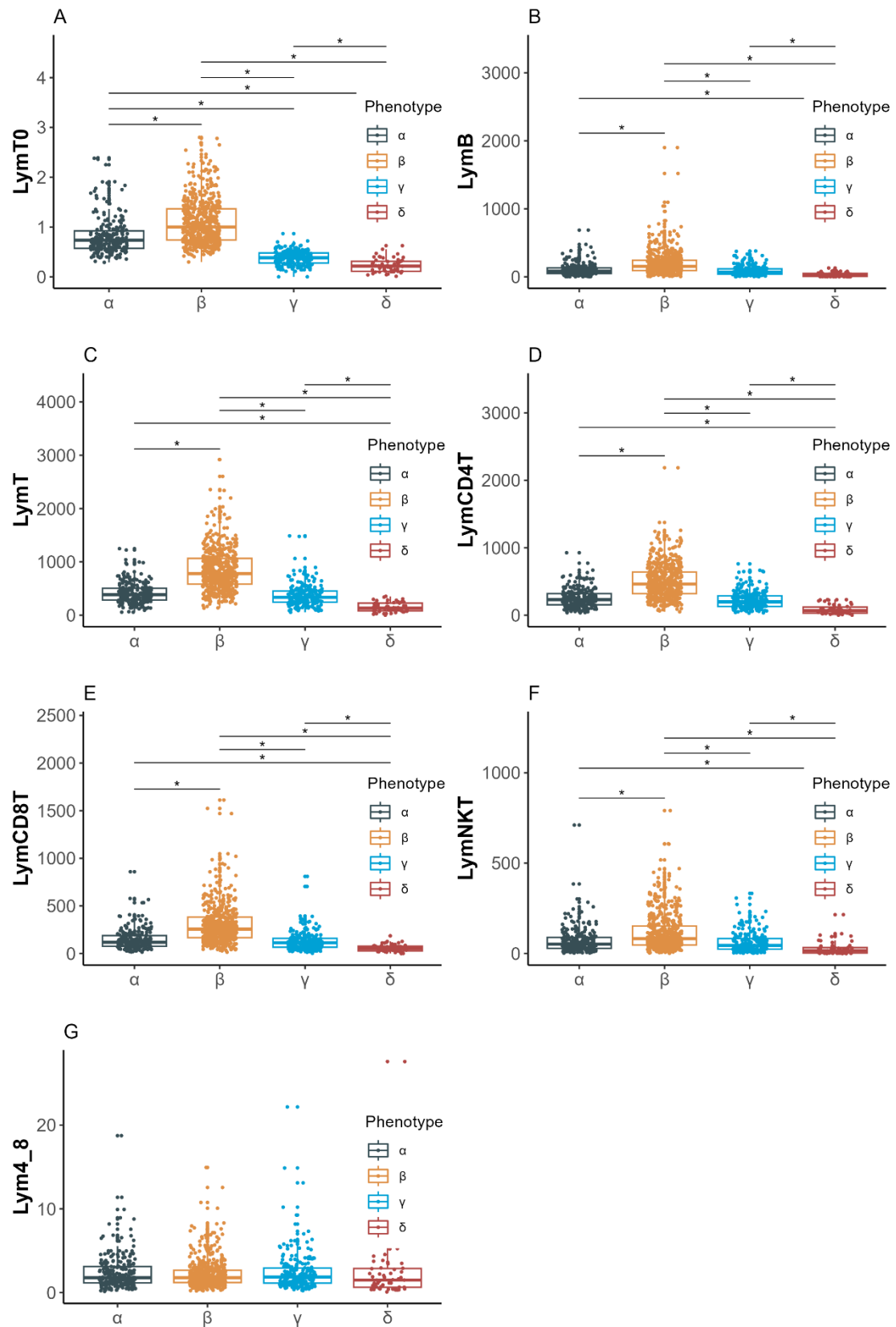


Figure S5. Comparison of lymphocyte subset counts among the four lymphocyte trajectory phenotypes in the prospective cohort. A–G represent the different

lymphocyte subsets (y-axis). LymT0, total lymphocyte count at intensive care unit admission; LymB, B-lymphocyte count; LymT, T-lymphocyte count; LymCD4T, CD4⁺ T-lymphocyte count; LymCD8T, CD8⁺ T-lymphocyte count; LymNK, natural killer lymphocyte count; Lym4_8, ratio of CD4⁺ to CD8⁺ T lymphocyte counts. The asterisk denotes statistical significance ($P < .005$).