

Supplementary Material

Supplementary Table 1. Presence of organ dysfunction and severity of dysfunction* for survivors and non-survivors by 28 days.

Organ Dysfunction Incidence by Day 28 (n, %)	<u>All Patients</u> (n=7897)	<u>Survivors</u> (n=7431)	<u>Non-survivors</u> (n=466)
Endocrinologic	5143 (65.1%)	4730 (62.4%)	413 (88.6%)
Cardiovascular	4384 (55.5%)	3957 (53.2%)	427 (91.6%)
Severe Cardiovascular	881 (11.2%)	617 (8.3%)	264 (56.7%)
Immunologic	4184 (53.0%)	3901 (52.5%)	283 (60.7%)
Neurologic	4156 (52.6%)	3742 (50.4%)	414 (88.8%)
Respiratory	3555 (45.0%)	3158 (42.5%)	397 (85.2%)
Severe Respiratory	1009 (12.8%)	750 (10.1%)	259 (55.6%)
Hematologic	3204 (40.6%)	2879 (38.7%)	325 (69.7%)
Severe Hematologic	351 (4.4%)	304 (4.1%)	47 (10.1%)
Renal	2898 (36.7%)	2620 (35.3%)	278 (59.7%)
Coagulation	994 (12.6%)	835 (11.2%)	159 (34.1%)
Liver	623 (7.9%)	437 (5.9%)	186 (39.9%)

*Severity grading based on PODIUM criteria is only available for cardiovascular, respiratory, and hematologic dysfunction

Supplementary Table 2. Association between two organ dysfunction interactions and mortality or persistent MOD.

<u>Combinations of two Organ Dysfunctions</u>	<u>Total (n, %)</u>	<u>Died (n=466)</u>	<u>p-value</u>	<u>Persistent MOD (n=1002)</u>	<u>p-value</u>
Coag+CV	518 (6.6%)	107 (20.7%)	0.26	166 (16.6%)	0.13
Coag+Endo	597 (7.6%)	107 (17.9%)	0.27	200 (20.0%)	0.15
Coag+Immuno	553 (7.0%)	81 (14.6%)	0.34	191 (19.1%)	0.86
Coag+Neuro	370 (4.7%)	88 (23.8%)	0.99	145 (14.5%)	0.89
Coag+Renal	354 (4.5%)	70 (19.8%)	0.91	137 (13.7%)	0.06
Coag+Resp	379 (4.8%)	102 (26.9%)	0.02	160 (16.0%)	0.89
CV+Endo	2603 (33.0%)	329 (12.6%)	<0.001*	476 (47.5%)	<0.001*
CV+Heme	1419 (18.0%)	237 (16.7%)	0.02	397 (39.6%)	0.86
CV+Immuno	1728 (21.9%)	202 (11.7%)	0.51	382 (38.1%)	0.54
CV+Liver	432 (5.5%)	155 (35.9%)	0.001*	140 (14.0%)	0.02
CV+Neuro	2154 (27.3%)	323 (15.0%)	<0.001*	472 (47.1%)	<0.001*
CV+Renal	1240 (15.7%)	202 (16.3%)	<0.001*	268 (26.7%)	0.14
CV+Resp	2007 (25.4%)	316 (15.7%)	<0.001*	480 (47.9%)	<0.001*
Endo+Heme	1683 (21.3%)	232 (13.8%)	0.06	466 (46.5%)	0.003*
Endo+Immuno	2399 (30.4%)	212 (8.8%)	0.98	469 (46.8%)	0.12
Endo+Liver	491 (6.2%)	149 (30.3%)	0.50	164 (16.4%)	0.79
Endo+Neuro	2258 (28.6%)	310 (13.7%)	<0.001*	480 (47.9%)	<0.001*
Endo+Renal	1642 (20.8%)	200 (12.2%)	0.05	321 (32.0%)	0.10
Endo+Resp	2001 (25.3%)	307 (15.3%)	<0.001*	484 (48.3%)	<0.001*
Heme+Immuno	1833 (23.2%)	188 (10.3%)	0.56	492 (49.1%)	0.007
Heme+Liver	433 (5.5%)	131 (30.3%)	0.31	161 (16.1%)	0.28
Heme+Neuro	1164 (14.7%)	211 (18.1%)	0.30	349 (34.8%)	<0.001*
Heme+Renal	964 (12.2%)	169 (17.5%)	<0.001*	295 (29.4%)	0.03
Heme+Resp	1060 (13.4%)	224 (21.1%)	<0.001*	360 (35.9%)	<0.001*
Immuno+Liver	329 (4.2%)	83 (25.2%)	<0.001*	126 (12.6%)	0.58
Immuno+Neuro	1522 (19.3%)	189 (12.4%)	0.68	355 (35.4%)	<0.001*
Immuno+Renal	1165 (14.8%)	132 (11.3%)	0.18	303 (30.2%)	<0.001*
Immuno+Resp	1376 (17.4%)	200 (14.5%)	0.02	359 (35.8%)	<0.001*
Liver+Neuro	439 (5.6%)	150 (34.2%)	0.02	147 (14.7%)	0.03
Liver+Renal	323 (4.1%)	113 (35.0%)	0.09	118 (11.8%)	0.92

Liver+Resp	387 (4.9%)	145 (37.5%)	0.06	148 (14.8%)	0.64
Neuro+Renal	1119 (14.2%)	189 (16.9%)	<0.001*	273 (27.2%)	0.03
Neuro+Resp	2296 (29.1%)	303 (13.2%)	0.81	557 (55.6%)	<0.001*
Renal+Resp	946 (12.0%)	193 (20.4%)	<0.001*	267 (26.6%)	0.09

*p<0.005 considered statistically significant.

Coag: coagulation

CV: cardiovascular

Endo: endocrinologic

Immuno: immunologic

Heme: hematologic

Neuro: neurologic

Resp: respiratory

Supplementary Table 3. Association between three organ dysfunction interactions and mortality or persistent MOD.

<u>Combined Organ Dysfunctions</u>	<u>All Patients (n=7897)</u>	<u>Died (n=466)</u>	<u>p-value</u>	<u>Persistent MOD (n=1002)</u>	<u>p-value</u>
Coag+CV+Endo	420 (5.3%)	100 (23.8%)	0.72	146 (14.6%)	0.67
Coag+CV+Immuno	356 (4.5%)	70 (19.7%)	0.11	127 (12.7%)	0.30
Coag+CV+Neuro	294 (3.7%)	86 (29.3%)	0.72	119 (11.9%)	0.17
Coag+CV+Renal	250 (3.2%)	64 (25.6%)	0.14	98 (9.8%)	0.44
Coag+CV+Resp	312 (4.0%)	95 (30.4%)	0.41	132 (13.2%)	0.34
Coag+Endo+Immuno	422 (5.3%)	73 (17.3%)	0.68	158 (15.8%)	0.70
Coag+Endo+Neuro	322 (4.1%)	84 (26.1%)	0.27	128 (12.8%)	0.003*
Coag+Endo+Renal	288 (3.6%)	65 (22.6%)	0.64	115 (11.5%)	0.12
Coag+Endo+Resp	327 (4.1%)	96 (29.4%)	0.93	141 (14.1%)	0.04
Coag+Immuno+Neuro	247 (3.1%)	57 (23.1%)	0.23	110 (11.0%)	0.04
Coag+Immuno+Renal	249 (3.2%)	49 (19.7%)	0.74	108 (10.8%)	0.05
Coag+Immuno+Resp	264 (3.3%)	69 (26.1%)	0.22	118 (11.8%)	0.89
Coag+Neuro+Renal	198 (2.5%)	54 (27.3%)	0.02	94 (9.4%)	0.53
Coag+Neuro+Resp	292 (3.7%)	85 (29.1%)	0.40	130 (13.0%)	0.004*
Coag+Renal+Resp	211 (2.7%)	63 (29.9%)	0.05	97 (9.7%)	0.14
CV+Endo+Heme	1026 (13.0%)	213 (20.8%)	0.18	322 (32.1%)	0.73
CV+Endo+Immuno	1217 (15.4%)	179 (14.7%)	0.71	311 (31.0%)	0.27
CV+Endo+Liver	387 (4.9%)	146 (37.7%)	0.93	130 (13.0%)	0.54
CV+Endo+Neuro	1488 (18.8%)	289 (19.4%)	0.61	374 (37.3%)	0.03
CV+Endo+Renal	912 (11.5%)	183 (20.1%)	0.59	221 (22.1%)	0.49
CV+Endo+Resp	1414 (17.9%)	285 (20.2%)	0.14	377 (37.6%)	<0.001*
CV+Heme+Immuno	890 (11.3%)	152 (17.1%)	0.24	279 (27.8%)	<0.001*
CV+Heme+Liver	336 (4.3%)	127 (37.8%)	0.96	122 (12.2%)	0.52
CV+Heme+Neuro	816 (10.3%)	201 (24.6%)	0.35	275 (27.4%)	0.29
CV+Heme+Renal	573 (7.3%)	156 (27.2%)	0.04	183 (18.3%)	<0.001*
CV+Heme+Resp	795 (10.1%)	206 (25.9%)	0.79	288 (28.7%)	0.63
CV+Immuno+Liver	249 (3.2%)	80 (32.1%)	0.43	96 (9.6%)	0.63
CV+Immuno+Neuro	897 (11.4%)	167 (18.6%)	0.28	266 (26.5%)	0.86
CV+Immuno+Renal	562 (7.1%)	113 (20.1%)	0.78	180 (18.0%)	0.01
CV+Immuno+Resp	879 (11.1%)	172 (19.6%)	0.60	274 (27.3%)	0.77
CV+Liver+Neuro	369 (4.7%)	148 (40.1%)	0.61	121 (12.1%)	0.01
CV+Liver+Renal	273 (3.5%)	112 (41.0%)	0.51	96 (9.6%)	0.30

CV+Liver+Resp	341 (4.3%)	142 (41.6%)	0.41	122 (12.2%)	0.001*
CV+Neuro+Renal	728 (9.2%)	176 (24.2%)	0.37	218 (21.8%)	0.24
CV+Neuro+Resp	1469 (18.6%)	283 (19.3%)	0.02	428 (42.7%)	0.77
CV+Renal+Resp	679 (8.6%)	178 (26.2%)	0.76	215 (21.5%)	1.0
Endo+Heme+Immuno	1073 (13.6%)	152 (14.2%)	0.39	352 (35.1%)	0.79
Endo+Heme+Liver	381 (4.8%)	124 (32.5%)	0.48	144 (14.4%)	0.65
Endo+Heme+Neuro	864 (10.9%)	188 (21.8%)	0.01	289 (28.8%)	0.43
Endo+Heme+Renal	693 (8.8%)	153 (22.1%)	0.05	234 (23.4%)	0.69
Endo+Heme+Resp	806 (10.2%)	198 (24.6%)	0.21	296 (29.5%)	0.18
Endo+Immuno+Liver	295 (3.7%)	79 (26.8%)	0.90	116 (11.6%)	0.50
Endo+Immuno+Neuro	1048 (13.3%)	164 (15.6%)	0.003*	290 (28.9%)	0.93
Endo+Immuno+Renal	813 (10.3%)	118 (14.5%)	0.23	233 (23.3%)	0.32
Endo+Immuno+Resp	995 (12.6%)	171 (17.2%)	0.002*	289 (28.8%)	0.02
Endo+Liver+Neuro	395 (5.0%)	141 (35.7%)	0.23	132 (13.2%)	0.009
Endo+Liver+Renal	294 (3.7%)	106 (36.1%)	0.23	109 (10.9%)	0.91
Endo+Liver+Resp	355 (4.5%)	138 (38.9%)	0.77	133 (13.3%)	0.003*
Endo+Neuro+Renal	755 (9.6%)	170 (22.5%)	0.87	216 (21.6%)	0.09
Endo+Neuro+Resp	1474 (18.7%)	274 (18.6%)	0.03	422 (42.1%)	0.005
Endo+Renal+Resp	695 (8.8%)	174 (25.0%)	0.97	215 (21.5%)	0.009
Heme+Immuno+Liver	281 (3.6%)	75 (26.7%)	0.42	115 (11.5%)	0.29
Heme+Immuno+Neuro	659 (8.3%)	135 (20.5%)	0.89	234 (23.4%)	0.88
Heme+Immuno+Renal	605 (7.7%)	112 (18.5%)	0.38	230 (23.0%)	0.17
Heme+Immuno+Resp	619 (7.8%)	146 (23.6%)	0.30	239 (23.9%)	0.13
Heme+Liver+Neuro	347 (4.4%)	124 (35.7%)	0.91	127 (12.7%)	0.73
Heme+Liver+Renal	268 (3.4%)	101 (37.7%)	0.52	102 (10.2%)	0.003*
Heme+Liver+Resp	316 (4.0%)	122 (38.6%)	0.90	128 (12.8%)	0.46
Heme+Neuro+Renal	497 (6.3%)	140 (28.2%)	0.84	178 (17.8%)	0.57
Heme+Neuro+Resp	817 (10.3%)	191 (23.4%)	0.62	298 (29.7%)	0.14
Heme+Renal+Resp	481 (6.1%)	146 (30.4%)	0.19	174 (17.4%)	0.05
Immuno+Liver+Neuro	257 (3.3%)	78 (30.4%)	0.58	105 (10.5%)	<0.001*
Immuno+Liver+Renal	196 (2.5%)	64 (32.7%)	0.57	83 (8.3%)	0.06
Immuno+Liver+Resp	226 (2.9%)	76 (33.6%)	0.32	103 (10.3%)	0.001*
Immuno+Neuro+Renal	517 (6.5%)	103 (19.9%)	0.10	179 (17.9%)	0.80
Immuno+Neuro+Resp	943 (11.9%)	162 (17.2%)	0.25	299 (29.8%)	0.90
Immuno+Renal+Resp	484 (6.1%)	110 (22.7%)	0.03	176 (17.6%)	0.56
Liver+Neuro+Renal	274 (3.5%)	107 (39.1%)	0.18	101 (10.1%)	0.80
Liver+Neuro+Resp	362 (4.6%)	141 (39.0%)	0.44	133 (13.3%)	<0.001*

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Liver+Renal+Resp	256 (3.2%)	105 (41.0%)	0.05	102 (10.2%)	0.64
Neuro+Renal+Resp	721 (9.1%)	170 (23.6%)	0.94	236 (23.6%)	0.17

*p<0.005 considered statistically significant.

Coag: coagulation

CV: cardiovascular

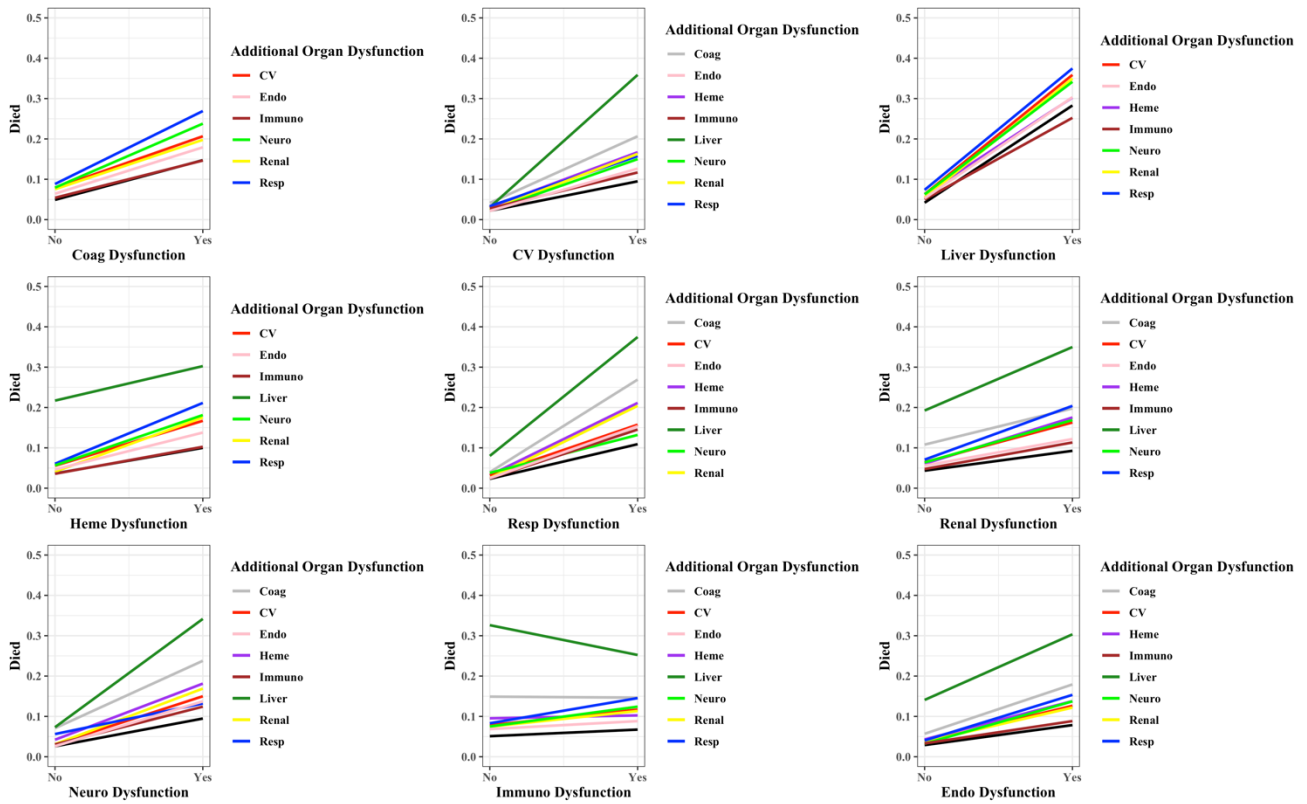
Endo: endocrinologic

Immuno: immunologic

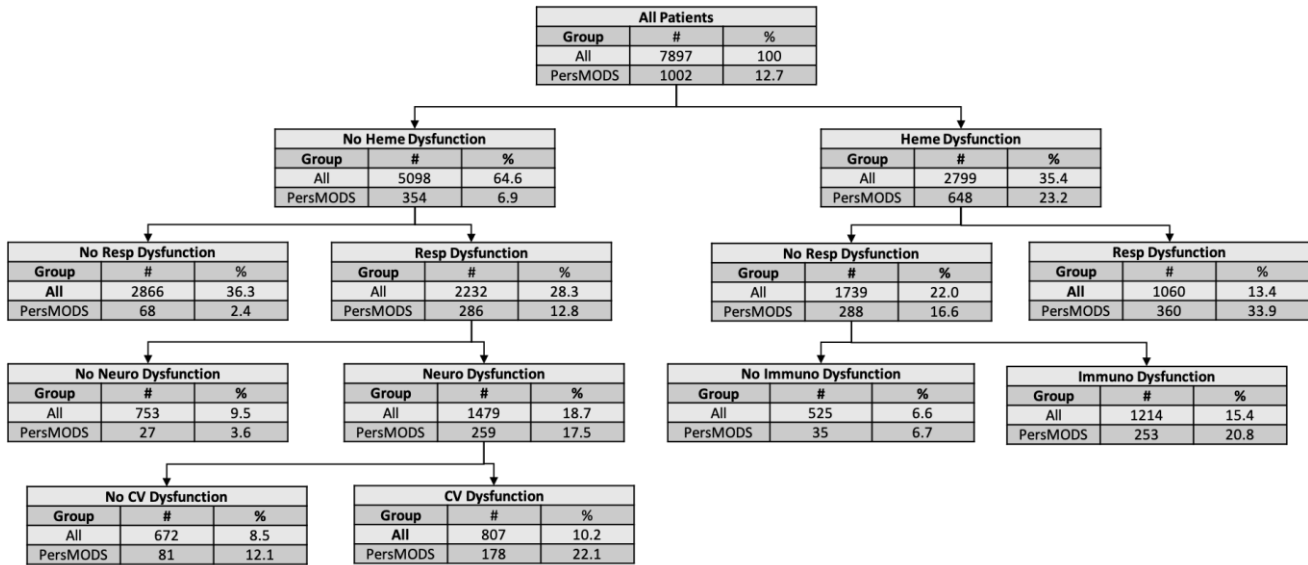
Heme: hematologic

Neuro: neurologic

Resp: respiratory



Supplementary Figure 1. Interaction plots for two organ dysfunctions and association with mortality. Black line represents single organ dysfunction, colored lines (per legend) represent interaction with second organ dysfunction. *Coag*: coagulation; *CV*: cardiovascular; *Endo*: endocrinologic; *Immuno*: immunologic; *Heme*: hematologic; *Neuro*: neurologic; *Resp*: respiratory



Supplementary Figure 2. Classification Tree for Persistent MODS using 10-fold cross validation. The top node of the decision tree, the root node, shows the total number of subjects in the cohort and the number and proportion of non-survivors. Each subsequent node shows the criterion for subsequent decisions, along with the number and proportion of patients with or without the organ dysfunction and the proportion who died. Terminal nodes show the risk for an individual with the preceding organ dysfunctions. AUROC = 0.74 (95% CI 0.70-0.78). *Coag*: coagulation; *CV*: cardiovascular; *Endo*: endocrinologic; *Immuno*: immunologic; *Heme*: hematologic; *Neuro*: neurologic; *Resp*: respiratory