Additional File 1: Supplementary Methods

Patient Enrolment and Sample Collection

A prospective, observational study was conducted at the Emergency Department (ED) of the Charité-Universitätsmedizin Berlin, Campus Benjamin Franklin (Berlin, Germany) from February until December 2019. Enrolment criteria were i) adult patients (≥18 years) presenting to the ED with clinically suspected acute infections, ii) at least one vital sign change (temperature >38°C or <36°C, respiratory rate >20/min, heart rate >90/min, systolic blood pressure <100mmHg or altered mental state), and iii) consent, including retroactive consent, by self or legal guardian. Suspicion of infection was determined by the triage nurses and treating physicians at the point of presentation to the ED. At enrolment, 2.5 mL of whole blood was collected in PAXgene® blood RNA tubes (PreAnalytix, Hombrechtikon, Switzerland) and then processed and stored at -80^{o}C following the manufacturer instructions.

Sample Processing

RNA was extracted from PAXgene Blood RNA tubes on the QiaCube(R) Connect platform with the RNeasy(R) Plus Micro Kit (all QIAGEN, Hilden, Germany). Expression of the 29-mRNAs was quantified from 150 ng of RNA input using the NanoString nCounter(R) SPRINT profiler (NanoString, Seattle, WA) with four housekeeping genes used for normalization. mRNA counts were used as input to the IMX-SEV-2 classifier.

Statistical Analysis

Linear regression with the IMX-SEV-2 score as an outcome variable and mortality, age, sex, infection status, and immunocompromised status as predictor variables was used to assess whether patient characteristics other than mortality status had an impact on the IMX-SEV-2 score. *P*-values were calculated using Mann-Whitney U and Fisher's Exact tests for continuous and nominal variables, respectively, and DeLong's method for comparing AUROCs. Statistical analyses were performed in R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). Receiver Operating Characteristics were calculated and plotted using the pROC package. Precision Recall Curves were calculated using the PRROC package, and bias-corrected and accelerated confidence intervals and tests for significant differences were performed with the boot package.

IMX-SEV-2 classifier development

The datasets used for classifier development are shown in Supplemental Table S5. We started with a set of 69 features: 1) gene expression for the individual 29 diagnostic markers, 2) geometric and arithmetic means (20 features for each type of mean) of subsets of the markers grouped based on high or low expression according to patient infection or 30-day mortality status (based on previous work[1-3]). We then processed these 69 gene expression features with the H2O.ai software suite (version 1.8)[4], generating an additional 171 features based on pairwise sums, differences, products and ratios of the original 69 features. We filtered these 240 features (69 expression features + 171 engineered feature combinations) such that no pair of features shared a pairwise Pearson correlation coefficient greater than 0.995. This filtration step resulted in 209 remaining features that were used for subsequent classifier development. We then selected the classifier for final validation using both grid and random sampling-based methods to search hyperparameter spaces of multiple classifier types (e.g., multi-layer perceptrons, support vector classifiers, etc.) as described previously[1]. In addition to model hyperparameters (e.g., value of LASSO penalty coefficient, if used), we treated the size of the feature set used for training as a model hyperparameter. We ranked each of the aforementioned 209 features according to their Pearson correlation with the outcome of interest (30-day mortality). In our hyperparameter tuning search, we considered a different subset of the top-ranking features (e.g., top 5, top 10, up to top 200) from this set of 209 features as input to the classifier being tuned. We evaluated each candidate classifier (a given top-ranking subset of features and model hyperparameter settings) in grouped five-fold cross-validation, training the classifier on each subset of four of the folds and generating predicted probabilities for the remaining fold. We used grouped five-fold cross-validation, restricting patients from each study to appear in only one of the five folds, to preserve study-specific structure and to give more realistic estimates of the model's generalization performance. We pooled the predicted probabilities across the five validation folds and computed the AUROC for 30-day mortality events. We found that a logistic regression classifier trained on the top 150 features achieved the highest AUROC (0.905, 95% CI 0.891–0.920) for 30-day mortality, and this classifier was called IMX-SEV-2. In Supplementary Fig. S3A, we show the ROC curve of IMX-SEV-2 as computed from the pooled predicted probabilities in cross-validation. Owing to class imbalance for 30-day mortality in our dataset (0.070 baseline rate of occurrence of 30-day mortality), we also show the precision-recall curve (AUPR = 0.428) in Supplementary Figure S3B.

The genes measured in the assay have been previously described [1]. Of the 29 mRNAs, 11 are used to determine infection severity (DEFA4, CD163, RGS1, PER1, HIF1A, SEPP1, C11orf74, CIT, LY86, TST, KCNJ2), while 18 are used in determining infection status (CEACAM1, ZDHHC19, C9orf95, GNA15, BATF, C3AR1, KIAA1370, TGFBI, MTCH1, RPGRIP1, HLA-DPB1, HK3, TNIP1, GPAA1, CTSB, IFI27, JUP, LAX1).

Supplemental Data

Internal ID	Age	Male	Lactate	qSOFA	NEWS2	In-Hospital Mortality	Multi-Organ Failure	Immuno-suppression	IMX-SEV-2
101	76	1	1.954	2	8	0	1	0	0.04181
102	82	1	7.215	1	6	0	0	0	0.05495
103	86	1	3.086	1	3	0	0	0	0.04740
104	51	0	1.443	1	8	0	0	0	0.02572
105	72	0	1.554	1	6	0	0	0	0.03886
106	78	1	2.153	1	0	0	0	0	0.03303
107	27	0	1.321	0	1	0	0	0	0.03889
108	64	1	3.441	1	9	0	1	0	0.07712
109	84	1	2.220	2	8	0	0	0	0.02681
110	78	1	1.110	0	3	0	0	0	0.03236
111	96	1	1.332	1	5	0	0	0	0.02506
112	68	1	2.031	2	9	0	1	1	0.02318
113	82	1	1.110	1	7	0	0	0	0.07727
114	85	1	1.521	2	9	0	0	0	0.02565
115	89	1	1.554	1	8	0	0	0	0.04154
116	61	1	2.442	2	5	0	1	0	0.07913
117	66	1	1.887	1	3	0	0	0	0.06303
118	31	0	0.888	0	1	0	0	0	0.02260
119	21	0	0.999	1	7	0	0	0	0.03953
120	80	0	1.332	0	3	0	0	1	0.05530
121	46	1	2.109	1	7	0	0	0	0.01447
122	57	0	2.220	0	4	0	0	0	0.01828
123	60	1	1.110	2	7	0	0	0	0.03067
124	60	1	1.665	0	5	0	0	0	0.02903
125	74	1	1.110	1	4	0	0	0	0.03487
126	38	0	1.110	1	6	0	0	0	0.01878
127	67	1	3.219	1	10	0	1	0	0.03942
129	61	1	1.332	0	3	0	0	0	0.02022
130	69	1	1.665	1	7	0	0	0	0.02205
131	70	0	2.120	0	5	0	0	0	0.02013
132	72	1	2.109	0	1	0	0	0	0.05120
133	74	0	4.773	2	10	0	1	1	0.04773
134	70	1	1.110	2	11	0	1	0	0.02505
135	68	1	5.550	2	14	0	1	0	0.19184
136	78	0	1.221	2	7	0	0	0	0.02166
137	70	1	1.776	0	4	0	0	0	0.03391
138	29	0	1.887	0	5	0	0	0	0.02404
139	77	0	1.554	0	5	0	0	0	0.04678
140	89	0	1.998	2	7	0	1	0	0.01779
141	72	0	0.999	1	4	0	0	0	0.03463

142	22	0	2.109	2	7	0	0	0	0.07394
143	57	0	1.665	1	2	0	0	1	0.04786
144	84	1	1.665	1	10	0	0	1	0.06629
145	66	1	2.109	1	8	0	1	1	0.38451
146	75	1	1.776	1	8	0	0	0	0.16116
147	67	1	2.775	0	7	0	0	1	0.06543
148	78	0	1.887	2	8	0	0	0	0.07184
149	88	1	2.553	2	7	0	0	0	0.02922
150	71	1	2.109	0	1	0	0	0	0.02198
151	64	1	1.865	0	1	0	0	0	0.02033
152	76	1	1.554	1	6	0	0	0	0.03446
153	39	0	2.109	0	2	0	0	1	0.02836
154	67	1	4.329	1	6	0	1	0	0.05180
155	74	1	1.443	0	2	0	0	1	0.06773
156	62	1	2.109	2	9	0	0	0	0.02323
157	81	1	1.221	0	3	0	0	0	0.05264
158	67	0	2.220	1	1	0	0	0	0.03099
159	73	0	1.998	1	4	0	0	0	0.09424
160	77	1	1.665	0	0	0	0	0	0.03875
161	64	0	2.331	1	6	0	0	0	0.04239
162	77	1	1.665	0	3	0	0	0	0.02657
163	74	1	2.997	1	7	0	0	0	0.05812
164	21	0	1.221	0	1	0	0	1	0.04815
165	68	1	1.443	0	6	0	0	0	0.02977
166	99	0	1.332	3	7	0	0	0	0.08471
167	38	0	2.753	1	5	0	0	0	0.04908
168	52	0	0.999	0	2	0	0	0	0.05839
169	58	0	2.553	1	5	1	0	1	0.09728
171	23	0	1.221	1	8	0	0	0	0.02196
172	80	1	1.443	3	9	0	0	0	0.03787
173	69	0	1.132	2	8	0	1	1	0.08229
174	64	0	1.465	0	2	0	0	0	0.03789
176	58	1	0.777	0	5	0	0	1	0.06177
177	85	1	1.221	0	0	0	0	0	0.01770
178	79	0	1.998	1	6	0	0	1	0.02088
179	80	0	0.888	0	3	0	0	0	0.02066
180	88	0	1.998	0	1	0	0	0	0.02289
181	84	0	2.442	1	3	0	1	1	0.08519
182	76	1	1.554	2	5	0	1	1	0.05425
183	69	0	1.443	0	0	0	0	0	0.02917
184	71	0	1.887	1	4	0	0	0	0.08753
185	57	0	2.553	0	4	0	1	0	0.06415
186	84	0	2.109	0	6	0	0	0	0.02016

187	82	1	0.888	1	8	0	0	0	0.06664
188	77	1	2.442	0	8	0	0	0	0.07746
189	84	0	2.664	1	7	0	0	0	0.04166
190	82	1	2.220	0	2	0	0	1	0.01683
191	85	1	1.665	3	11	0	1	0	0.02259
192	77	1	10.101	0	6	0	0	1	0.03404
193	91	1	3.330	0	1	0	0	1	0.02791
194	66	0	0.999	0	1	0	0	0	0.02656
195	79	0	2.109	3	13	0	1	0	0.15894
196	92	1	2.997	3	13	1	1	0	0.11786
197	81	0	1.110	1	5	0	0	0	0.03741
198	80	0	3.885	0	1	0	0	0	0.03642
199	77	0	2.553	2	12	0	1	0	0.03680
200	80	0	3.552	2	4	0	0	1	0.02177
201	80	1	1.776	1	6	0	0	1	0.05215
202	76	0	3.164	0	4	0	0	1	0.03473
203	78	0	1.665	1	6	1	1	1	0.05404
204	87	1	2.775	0	5	0	0	0	0.03677
205	54	1	1.765	0	2	0	0	0	0.02839
206	79	0	1.721	2	8	0	0	0	0.05577
207	82	1	3.996	1	8	0	1	0	0.08450
208	78	0	3.663	2	6	0	0	0	0.07193
209	64	0	2.109	1	8	0	0	0	0.06765
210	61	0	2.764	0	6	1	1	1	0.08731
211	70	1	6.771	0	4	0	0	0	0.05907
212	26	1	2.065	0	2	0	0	0	0.02250
213	40	1	0.888	0	3	0	0	0	0.01672
214	42	1	1.554	0	5	0	0	0	0.01856
215	33	0	2.031	1	8	0	0	0	0.03223
216	81	1	4.440	0	1	0	0	0	0.06045
217	81	0	1.554	0	0	0	0	0	0.08680
218	74	0	3.330	1	9	0	0	0	0.03515
219	56	0	1.543	0	2	0	0	0	0.01294
220	59	0	0.777	1	4	0	0	0	0.02642
221	26	0	1.554	2	8	0	1	0	0.02321
222	83	1	3.996	0	2	0	0	1	0.03722
223	82	1	0.999	0	1	0	0	0	0.02095
224	62	1	3.774	1	4	0	1	0	0.03145
225	70	1	1.332	1	4	0	0	0	0.02447
226	37	0	0.777	2	9	0	1	1	0.03441
227	65	1	2.886	2	14	0	0	0	0.04183
228	24	1	1.332	0	2	0	0	0	0.04317
229	75	1	1.887	1	6	0	0	1	0.03559

230	77	0	1.332	1	7	0	0	1	0.06693
231	45	1	1.776	1	11	0	0	1	0.11739
232	76	1	1.665	1	8	0	0	0	0.02614
233	84	1	2.109	0	0	0	0	0	0.04452
234	89	1	1.332	1	8	0	0	0	0.04274
235	56	1	1.920	0	3	0	0	1	0.12549
236	86	1	2.331	2	7	0	0	0	0.02438
237	74	1	2.509	2	6	0	0	0	0.02546
238	81	1	2.553	2	5	0	1	0	0.02926
239	74	1	1.554	2	9	0	0	0	0.03053
240	37	1	2.442	0	3	0	0	1	0.02534
241	85	0	3.996	2	13	1	0	0	0.19245
242	32	1	2.109	0	1	0	0	0	0.03795
243	76	1	1.887	0	4	0	0	0	0.03081
244	80	1	1.221	0	0	0	0	1	0.01705
245	75	1	1.110	0	1	0	0	0	0.03896
246	92	1	1.887	1	4	0	0	0	0.03436
247	56	0	0.999	0	1	0	0	0	0.02245
248	58	1	1.998	0	1	0	0	0	0.02344
249	63	1	0.888	2	9	0	0	0	0.06944
250	48	1	1.587	0	4	0	0	0	0.01334
251	37	0	0.555	2	7	0	0	1	0.03166
252	75	1	5.106	2	14	0	1	0	0.12008
253	60	0	3.219	1	5	0	0	0	0.02468
254	55	0	0.888	0	3	0	0	1	0.01809
255	36	1	1.665	1	5	0	0	0	0.08069
256	73	1	1.665	0	3	0	0	0	0.03110
257	86	0	5.106	2	14	0	1	0	0.31761
258	65	1	2.997	2	10	0	0	0	0.07096
259	55	1	5.439	0	0	0	0	0	0.02053
260	77	1	4.995	1	10	1	1	0	0.05121
261	56	0	3.552	2	12	0	1	0	0.05706
262	62	0	2.220	1	13	0	0	0	0.05330
264	88	0	3.663	2	13	1	1	0	0.24227
265	84	0	1.732	0	5	0	0	0	0.03426
266	51	1	1.443	0	2	0	0	0	0.04498
267	64	0	0.888	0	6	0	0	0	0.03154
268	77	1	3.552	0	7	0	0	0	0.18205
269	89	0	1.188	1	10	0	0	0	0.02027
270	41	0	1.665	0	4	1	1	0	0.03828
271	23	1	1.676	0	13	0	0	0	0.01344
272	78	1	1.887	2	9	0	0	1	0.07623
273	74	1	1.887	0	2	0	0	0	0.02967

274	88	0	2.220	2	10	0	0	0	0.03848
275	83	1	5.772	2	12	0	0	0	0.13243
276	57	0	n.d.	1	5	0	0	0	0.05810
277	78	0	n.d.	0	4	0	0	0	0.06554
278	84	1	n.d.	2	11	0	0	1	0.06928
279	55	1	1.443	0	1	0	0	0	0.02556
280	72	0	0.888	1	2	0	0	0	0.03221
281	74	0	3.108	2	15	1	1	0	0.08476
282	74	1	1.443	0	1	0	0	0	0.03544
283	87	1	1.332	2	5	0	0	0	0.02580
284	77	1	2.331	2	7	0	0	0	0.04976
285	71	1	3.441	1	4	0	0	0	0.05685
286	34	0	0.888	0	2	0	0	0	0.02676
287	36	0	1.554	0	3	0	0	0	0.01869
288	73	1	1.443	1	5	0	0	0	0.01550
289	89	1	n.d.	1	5	0	0	0	0.02657
290	53	0	1.632	0	3	0	0	0	0.06125
291	84	0	4.329	2	8	1	1	0	0.18934
292	72	1	1.554	0	3	0	0	0	0.02007
293	75	0	1.221	1	4	0	0	1	0.03212
294	86	0	3.441	3	11	0	0	0	0.07036
295	75	1	n.d.	0	6	0	1	1	0.01852
296	78	0	1.865	0	2	0	0	1	0.06846
297	54	1	1.443	2	10	0	0	0	0.03155
298	70	1	0.555	1	7	0	0	1	0.05787
299	94	1	4.107	2	10	1	1	0	0.08486
300	83	1	2.109	1	8	0	0	0	0.04386
301	71	1	2.331	2	3	0	1	0	0.15474
302	74	1	5.328	2	13	0	0	0	0.16342
303	49	0	1.665	0	3	0	0	0	0.02107
304	76	1	1.443	1	10	0	1	0	0.03827
305	52	0	n.d.	1	3	0	0	0	0.02005
306	71	1	1.665	0	2	0	0	1	0.03010
307	22	1	1.110	0	2	0	0	0	0.01349
308	22	0	1.554	0	2	0	0	0	0.02808
309	32	1	1.976	1	7	0	0	0	0.01972
311	71	0	2.697	1	4	0	0	0	0.02517
312	81	1	5.106	1	6	0	0	0	0.06342
313	75	1	2.220	3	10	0	0	0	0.04715
314	61	1	2.031	0	3	0	0	0	0.02063
315	74	1	1.765	1	7	0	0	0	0.10541
316	78	1	n.d.	0	3	0	0	0	0.03852
317	81	1	3.885	1	12	0	0	0	0.28514

318	69	0	1.443	2	9	0	0	1	0.03738
319	70	1	2.065	0	1	0	0	0	0.01701
320	86	0	2.997	1	8	0	0	0	0.08322
321	48	0	3.630	1	7	0	1	0	0.13469
322	82	0	1.110	0	2	0	0	0	0.01805
323	92	1	1.665	0	5	0	0	0	0.11392
324	79	1	0.777	1	8	0	1	0	0.06744
325	71	1	1.110	0	0	0	0	0	0.02575
326	78	1	1.776	0	4	0	0	1	0.09659
327	86	0	1.998	0	4	0	0	1	0.05651
328	59	0	1.110	0	1	0	0	0	0.01774
329	92	0	1.554	2	6	0	0	0	0.04228
330	49	0	2.109	0	4	0	0	0	0.02140
331	59	1	9.102	3	10	1	1	0	0.29027
332	32	0	1.110	0	2	0	0	0	0.04929
333	25	1	1.443	0	1	0	0	0	0.01655
334	27	0	1.221	1	5	0	0	1	0.01886
335	71	0	0.999	0	0	0	0	1	0.02140
336	77	0	3.663	1	5	1	1	0	0.08419
338	67	1	3.552	3	15	0	1	0	0.14123
339	87	1	3.108	1	13	0	0	0	0.08635
340	81	1	3.608	1	8	0	0	0	0.03952
341	33	1	2.220	1	6	0	1	0	0.04397
342	87	1	1.221	1	5	0	0	0	0.03806
343	45	1	1.332	0	2	0	0	1	0.03195
344	94	1	1.221	0	5	0	0	0	0.01582
345	83	0	2.331	2	11	0	1	0	0.06073
346	80	1	1.887	1	4	0	0	1	0.05933
347	27	1	1.332	0	4	0	0	0	0.01884
348	80	1	1.776	0	2	0	0	0	0.01481
349	19	1	2.220	0	1	0	0	0	0.01687
350	82	0	2.298	3	12	0	0	1	0.05685
351	78	0	1.332	0	0	0	0	0	0.03223
352	56	1	2.331	0	6	0	0	1	0.04101
353	80	1	1.965	0	6	0	0	0	0.04711
354	40	0	1.776	0	7	0	0	0	0.04095
355	29	0	1.110	0	0	0	0	0	0.01553
356	83	1	2.109	2	15	0	1	0	0.02177
357	80	1	1.332	2	9	0	0	0	0.02161
358	28	1	2.442	0	4	0	0	0	0.01298
359	67	1	1.776	1	5	0	0	0	0.02483
360	65	1	1.443	1	7	0	0	1	0.11533
361	76	1	2.664	2	7	1	1	0	0.07574

362	18	0	n.d.	0	2	0	0	0	0.03671
363	77	1	1.554	2	5	0	0	1	0.02947
364	80	0	15.984	2	8	1	1	0	0.32225
365	80	0	4.107	1	13	0	0	0	0.07308
366	78	0	2.775	2	5	0	0	0	0.08791
367	75	1	n.d.	0	5	0	0	0	0.04593
368	71	1	9.713	1	7	0	0	0	0.08555
370	84	0	1.665	1	10	0	0	0	0.07512
371	54	1	2.997	0	10	0	1	0	0.07247
372	70	1	2.553	1	10	0	0	0	0.05554
373	79	0	1.332	0	1	0	0	0	0.02119
374	30	0	5.961	1	5	0	0	0	0.03121
375	75	0	4.551	3	6	0	0	0	0.02511
376	79	1	6.549	2	12	1	1	0	0.23757
377	35	0	1.554	0	5	0	0	0	0.01512
378	77	0	1.665	0	3	0	0	0	0.03022
379	61	0	1.809	2	6	0	0	0	0.02229
380	86	1	1.776	1	9	0	0	1	0.08178
381	57	1	1.299	0	3	0	0	0	0.02495
382	75	1	2.442	1	10	0	1	1	0.12841
383	98	1	2.220	2	7	0	0	0	0.06796
384	25	1	2.020	1	1	0	0	1	0.01658
385	27	0	1.110	1	1	0	0	0	0.01677
386	70	1	3.441	2	9	0	0	1	0.06127
387	84	1	4.662	1	12	0	0	0	0.06395
388	53	1	2.331	2	12	0	1	0	0.04894
389	45	1	2.142	0	5	0	0	1	0.04354
390	51	1	2.331	0	3	0	0	0	0.04203
391	78	1	2.109	1	4	0	0	0	0.03210
392	82	1	1.998	1	6	0	0	0	0.06512
393	64	1	1.998	0	3	0	0	1	0.16962
394	72	0	1.443	0	0	0	0	0	0.02813
395	79	1	1.665	0	1	0	0	1	0.03976
396	34	0	2.331	0	3	0	0	0	0.01668
397	76	0	1.332	0	1	0	0	1	0.02628
398	69	1	5.439	1	7	0	0	1	0.06959
399	72	1	3.996	2	9	0	0	0	0.02944
400	25	1	1.665	0	4	0	0	1	0.02691
401	76	0	1.776	2	11	0	0	0	0.03452
402	57	1	2.198	0	5	0	0	0	0.05809
403	34	0	1.332	0	4	0	0	1	0.02100
404	94	1	7.215	1	10	1	1	0	0.13577
405	48	0	n.d.	0	0	0	0	0	0.01415

406	63	1	1.221	0	3	1	0	0	0.02282
407	68	0	2.808	1	11	1	1	1	0.52222
408	71	1	1.654	0	4	0	0	0	0.03456
409	58	1	2.331	1	9	0	1	0	0.39159
410	72	0	n.d.	0	3	0	0	0	0.02842
411	58	0	2.220	0	8	0	0	0	0.05157
412	87	1	1.443	1	6	0	0	1	0.05963
413	88	0	1.554	2	12	1	1	0	0.07390
414	79	0	2.109	0	2	0	0	0	0.05620
415	34	0	1.088	0	3	0	0	0	0.03279
416	60	0	1.243	1	6	0	0	0	0.01975
417	78	0	2.109	0	7	1	1	0	0.08906
418	89	0	1.476	1	6	0	0	0	0.03436
419	77	1	1.221	1	5	1	1	0	0.03335

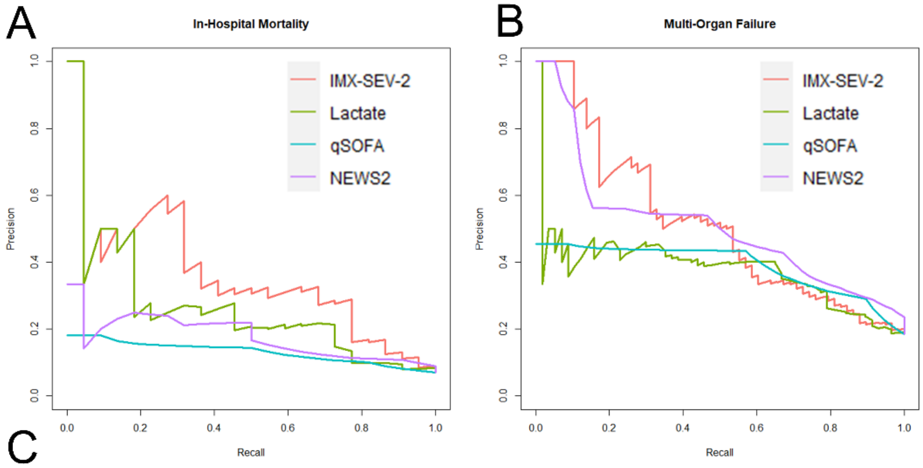
Supplemental Table S1: Additional Patient Characteristics

Characteristics	All (n=312)	Survival and/or Discharge n=290 (92.9%)	In-Hospital Mortality n=22 (7.1%)	*p*-values
Age [years]	72.5 (57.0, 80.0)	72.0 (57.0, 80.0)	77.5 (69.5, 84.8)	**0.02**
Sex [female]	132 (42.3%)	119 (41.0%)	13 (59.1%)	0.12
Vital Signs at presentation				
qSOFA ≥2	76 (24.4%)	65 (22.4%)	11 (50.0%)	**<0.01**
NEWS2	5 (3, 8)	5 (3, 8)	9 (6, 12)	<0.01
MEWS	4 (2, 5)	4 (2, 5)	4 (4, 7)	<0.01
Biomarkers				
Procalcitonin [µg/L]	305; 0.3 (0.1, 1.1)	283; 0.3 (0.1, 0.9)	1.7 (0.3, 26.6)	**<0.01**
Lactate [mmol/L]	301; 1.9 (1.4, 2.5)	279; 1.8 (1.4, 2.3)	3.1 (2.2, 4.3)	**<0.01**
IMX-SEV-2	0.04 (0.03, 0.07)	0.04 (0.03, 0.06)	0.09 (0.07, 0.19)	**<0.01**
Infection Outcome and Focus				
Bacterial Infection*	239 (76.6%)	219 (75.5%)	20 (90.9%)	0.12
Viral Infection*	86 (27.6%)	83 (28.6%)	3 (13.6%)	0.15
No Infection	32 (10.3%)	30 (10.3%)	2 (9.1%)	1.00
Pulmonary Focus	90 (28.8%)	87 (30.0%)	3 (13.6%)	0.14
Urogenital Focus	58 (18.6%)	58 (20.0%)	0 (0.0%)	**0.02**
Intraabdominal Focus	13 (4.2%)	11 (3.8%)	2 (9.1%)	0.23
Soft tissue/skin/bone Focus	11 (3.5%)	11 (3.8%)	0 (0.0%)	1.00
Blood/Catheter Focus	9 (2.9%)	8 (2.8%)	1 (4.5%)	0.49
CNS Focus	5 (1.6%)	4 (1.4%)	1 (4.5%)	0.31
No Clear or Multiple Foci	94 (30.1%)	81 (27.9%)	13 (59.1%)	**<0.01**
Outcomes				
Mechanical Ventilation	21 (6.7%)	13 (4.5%)	8 (36.4%)	**<0.01**
72h multi-organ failure	58 (18.6%)	39 (13.4%)	19 (86.4%)	**<0.01**
ICU Admission	71 (22.8%)	56 (19.3%)	15 (68.2%)	**<0.01**
90-day all-cause mortality	43 (13.8%)	21 (7.2%)	22 (100.0%)	**<0.01**

Continuous variables are presented with median and interquartile range and compared using Mann-Whitney U Test. Nominal variables are presented with frequency and column percentage, and compared using Fisher's Exact Test. The number of cases with valid data is shown for variables with missing data; qSOFA = Quick Sequential Organ Failure Assessment; NEWS2 = National Early Warning Score 2; CNS = Central Nervous System. *Includes bacterial-viral co-infections.

Table S2. List of reasons patients were considered to be immunosuppressed

Causes of Immunosuppression
Chemotherapy within the last 6 months
Hemato-oncological disease
High-dose systemic steroid therapy
Methotrexate therapy
Azathioprine therapy
Neutropenia (absolute neutrophil count <500/nl)



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	In-Hospital Mortality	Multi-Organ Failure within 72h
IMX-SEV-2	0.36 (0.19-0.58)	0.51 (0.39-0.63)
Lactate	0.26 (0.12-0.47)	0.38 (0.27-0.51)
qSOFA	0.13 (0.07-0.27)	0.39 (0.28-0.51)
NEWS2	0.18 (0.09-0.47)	0.51 (0.36-0.63)

Supplemental Figure S1. Precision Recall Curves of IMX-SEV-2 compared to SOC parameters.

Table S3. Accuracy of IMX-SEV-2 and comparators using single thresholds.

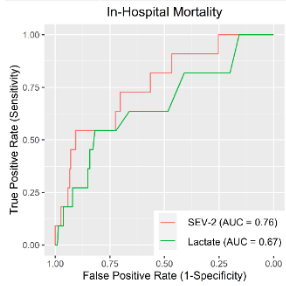
	In-Hospital Mortality		Multi-Organ Failure within 72h	
Biomarker (threshold)	Died n = 22	Survived n = 290	MOF n = 58	No MOF n = 254
	LR+	LR-	LR+	LR-
IMX-SEV-2 (≥ 0.042)	2.14	0.23	1.96	0.44
IMX-SEV-2 (≥ 0.157)	9.23	0.71	8.03	0.83
Lactate (≥2 mmol/l)	1.78	0.40	1.90	0.42
qSOFA (≥2)	2.23	0.64	3.36	0.52
NEWS2 (≥5, or ≥3 for any single category)	1.51	0.23	1.72	0.12
NEWS2 (≥7)	1.88	0.50	2.45	0.37
	Sens.	Spec.	Sens.	Spec.
IMX-SEV-2 (≥ 0.042)	86.4%	59.7%	72.4%	63.0%
IMX-SEV-2 (≥ 0.157)	31.8%	96.6%	19.0%	97.6%
Lactate (≥2 mmol/l)	77.3%	56.6%	74.1%	61.0%
qSOFA (≥2)	50.0%	77.6%	56.9%	83.1%
NEWS2 (≥5, or ≥3 for any single category)	90.9%	39.7%	94.8%	44.9%
NEWS2 (≥7)	68.2%	63.8%	74.1%	69.7%

qSOFA Assessment at Presentation
N=312

qSOFA < 2
n=236

Died n=11 | **Survived** n=225

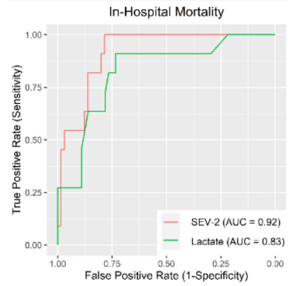
Band	Mortality	Survival
High	1	6
Moderate	7	79
Low	3	140



qSOFA ≥ 2
n=76

Died n=11 | **Survived** n=65

Band	Mortality	Survival
High	6	4
Moderate	5	28
Low	0	33

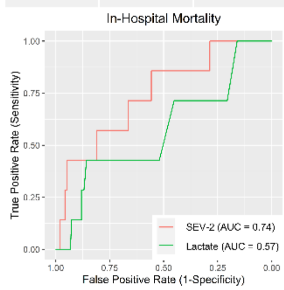


NEWS Assessment at Presentation
N=312

NEWS < 7
n=192

Died n=7 | **Survived** n=185

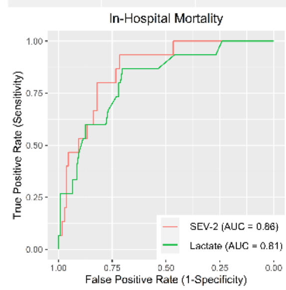
Band	Mortality	Survival
High	0	1
Moderate	4	54
Low	3	130



NEWS ≥ 7
n=120

Died n=15 | **Survived** n=105

Band	Mortality	Survival
High	7	9
Moderate	8	53
Low	0	43



Supplemental Figure S2. Decision Tree for Combining qSOFA (A) or NEWS (B) and IMX-SEV-2

Table S4: Subgroup effect analysis by linear regression with IMX-SEV-2 as dependent variable

Marker	Estimate	Standard Error	*P*-value
(Intercept)	0.0027	0.0232	0.9063
In-Hospital Mortality	0.0733	0.0189	0.0001
Multi-Organ Failure	0.0476	0.0128	0.0003
Age	0.0002	0.0003	0.4448
Immunocompromised	0.0190	0.0122	0.1217
Male Sex	0.0016	0.0096	0.8706
Bacterial infection	0.0289	0.0169	0.0895
Viral infection	0.0113	0.0128	0.3821

Study identifier	First author	Study description	N	Age [years]	Female (%)	Platform	Country	Mortality (%)
E-MEXP-3589	Almansa	Patients hospitalized with COPD exacerbation	27	70.1[a]	6 (22)[b]	Agilent	Spain	0 (0)
E-MTAB-1548	Almansa	Surgical patients with sepsis (EXPRESS)	140	Median 72 (IQR 61-78)	44 (31)[b]	Agilent	Spain	12 (9)
E-MTAB-3162	van de Weg	Patients with dengue	21	Median 20 (IQR 17-28)	10 (48)	Affymetrix	Indonesia	0 (0)
GSE13015 (GPL6102)	Pankla	Sepsis, many cases from burkholderia	45	Median 54 (IQR 48-61)	19 (42)	Illumina	Thailand	13 (29)
GSE13015 (GPL6947)	Pankla	Sepsis, many cases from burkholderia	15	Median 49 (IQR 43.5-59.5)	9 (60)	Illumina	Thailand	7 (47)
GSE21802	Bermejo-Martin	Pandemic H1N1 in ICU	10	unknown	unknown	Illumina	Canada	2 (20)
GSE22098	Berry	Patients with active TB and other IDs	193	Median 16 (IQR 11-26)	134 (69)	Illumina	UK	0 (0)
GSE25504 (GPL13667)	Smith	Neonatal sepsis	12	Median 0 (IQR 0-0)	4 (33)	Affymetrix	UK	1 (8)
GSE25504 (GPL6947)	Smith	Neonatal sepsis	21	Median 0 (IQR 0-0)	10 (48)	Illumina	UK	1 (5)
GSE27131	Berdal	Severe H1N1	7	Median 38 (IQR 33-50)	1 (14)	Affymetrix	Norway	2 (29)
GSE28991	Naim	Acute dengue	11	unknown	unknown	Illumina	unknown	0 (0)
GSE30119	Banchereau	Patients with active TB and other IDs	59	Median 6.5 (IQR 1.92-11)	25 (42)	Illumina	USA	0 (0)
GSE32707	Dolinay	Critically ill patients in Brigham \& Women's ICU	69	Median 57 (IQR 46-66)	34 (49)	Illumina	USA	25 (36)
GSE40012	Parnell	Bacterial or influenza A pneumonia or SIRS	39	Median 58 (IQR 44-66)	18 (46)	Illumina	Australia	5 (13)
GSE40165	Nguyen	Children and adolescents with dengue	123	Median 12 (IQR 10-14)	38 (31)	Illumina	Vietnam	0 (0)
GSE40396	Hu	Febrile young children	30	Median 0.92 (IQR 0.33-1.6)	13 (43)	Illumina	USA	0 (0)
GSE40586	Lill	Community-acquired bacterial meningitis	15	Median 57 (IQR 53-70.5)	unknown	Affymetrix	Estonia	2 (13)
GSE42026	Herberg	Children with H1N1/09, RSV or bacterial infection	59	Median 1.25 (IQR 0.38-4)	26 (44)	Illumina	UK	0 (0)
GSE47655	Stone	Acute anaphylaxis	6	unknown	unknown	Affymetrix	Australia	0 (0)
GSE51808	Kwissa	Dengue patients	28	unknown	unknown	Affymetrix	Thailand	0 (0)
GSE54514	Parnell	Critically ill septic patients	19	Median 65 (IQR 46-76)	11 (58)	Illumina	Australia	4 (21)
GSE57183	Senoi	SJIA patients	11	Median 3.6 (IQR 3.3-7.3)	6 (55)	Illumina	USA	0 (0)
GSE60244	Suarez	Lower respiratory tract infections	118	Median 62 (IQR 50-76)	69 (58)	Illumina	USA	0 (0)
GSE63881	Hoang	Kawasaki disease	171	Median 2.75 (IQR 1.42-4.25)	69 (40)	Illumina	USA	0 (0)
GSE64456	Mahajan	Febrile infants (60 days of age and younger)	279	Median 0.10 (IQR 0.06-0.13)	123 (44)	Illumina	USA	0 (0)

GSE65682	Scicluna	Suspected but negative for CAP	106	Median 63.5 (IQR 52.3-72.8)	44 (42)	Affymetrix	Netherlands	23 (22)
GSE66099	Sweeney	Pediatric ICU (sepsis, septic shock, or SIRS)	229	Median 2.5 (IQR 1.1-6.1)	90 (39)	Affymetrix	USA	28 (12)
GSE67059	Heinonen	Children with HRV infection	80	Median 0.83 (IQR 0.3-1.29)	27 (34)	Illumina	USA	0 (0)
GSE68310	Zhai	Outpatients with acute respiratory viral infections	104	Median 21.0 (IQR 20.1-22.8)	54 (52)	Illumina	USA	0 (0)
GSE72810	Herberg	Children with H1N1/09, RSV or bacterial infection	72	Median 1.79 (IQR 0.56-4.56)	31 (43)	Illumina	UK	0 (0)
GSE73461	Wright	Children with various IDs	404	Median 2.71 (IQR 0.83-8.04)	177 (44)	Illumina	UK	0 (0)
GSE77087	de Steenhuijsen Piters	Children with RSV infection	41	Median 0.45 (IQR 0.14-0.69)	16 (39)	Illumina	USA	0 (0)
GSE82050	Tang	Moderate and severe influenza infection	24	Median 64.5 (IQR 48.5-74.3)	9 (38)[b]	Agilent	Germany	0 (0)
GSE95233	Venet	Septic shock	51	Median 66 (IQR 53.5-73.5)	18 (35)[b]	Affymetrix	France	17 (33)
GSE103842	Rodriguez-Fernandez	Children with RSV infection	62	Median 0.25 (IQR 0.17-0.44)	23 (37)	Illumina	USA	0 (0)
AUS-NS	Tang	Patients with infections; primarily influenza	587	Median 54 (IQR 34.2-68)	329 (56)	NanoString	Australia	33 (6)

Table S5: Characteristics and composition of training studies for IMX-SEV-2.

ID = Infectious Disease; COPD = Chronic Obstructive Pulmonary Disease; ICU = Intensive Care Unit, CAP = Community-Acquired Pneumonia; SIRS = Systemic Inflammatory Response Syndrome; TB = Tuberculosis; SJIA = Systemic Juvenile Idiopathic Arthritis; HRV = Human Rhinovirus; RSV = Respiratory Syncytial Virus. [a]Study description is taken from the study's corresponding publication and includes some patients that were excluded from the training set. [b]Numbers and percentages shown reflect the fact that some patients in the study had unknown/unreported sex.

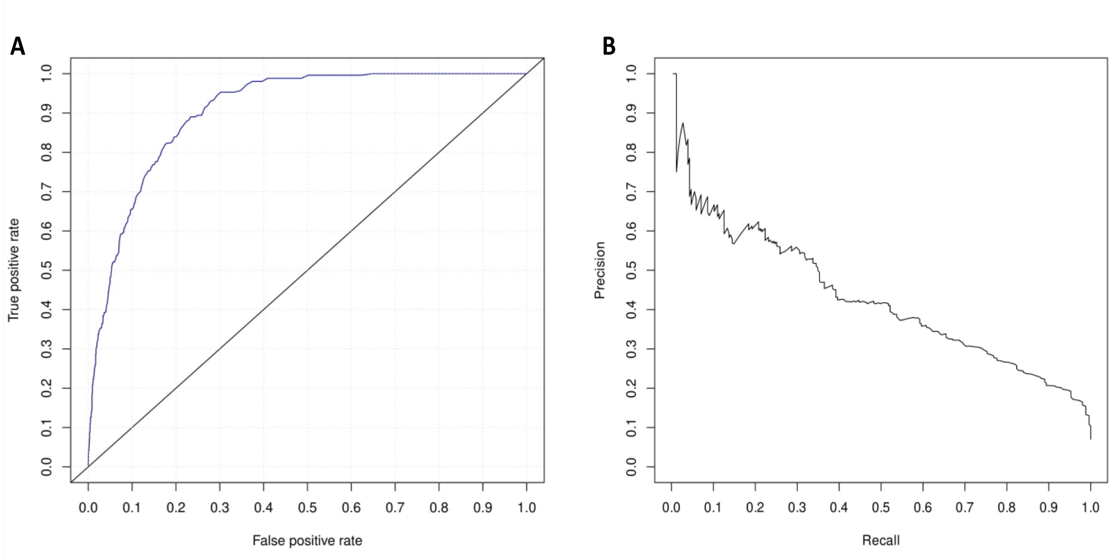


Figure S3. Shown are the receiver operating characteristic (A) and precision-recall (B) curves for the IMX-SEV-2 classifier. Both curves are based on pooled predicted probabilities from the five folds of grouped cross-validation.

Supplementary References

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