SUPPLEMENTAL DOCUMENT

Cardiovascular and Autonomic Phenotypes Reveal Distinct Mechanisms of Sepsis Decompensation via Deep Learning

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Online Data Supplement Information

Supplemental Table E1. Summary of selected ECG-derived physiomarkers after the preprocessing step in our study. Abbreviations – F.N.: feature number; Summary statistics: m = mean; p25 = 25th percentile; p75 = 75th percentile; s = skewness; e = entropy.

F.N.	Selected Base Feature (stats)	Description	Unit
1–5	ECG_T_rr_ms (m, p25, p75, s, e)	RR interval between successive R-peaks	ms
6	ECG_HR_bpm (s)	Asymmetry of heart rate distribution	bpm
7–11	ECG_edr_rate_Bpm (m, p25, p75, s, e)	ECG-derived respiratory rate	breaths/min
12–14	ECG_atrialSys_phase (m, s, e)	Temporal phase of atrial systole	ms
15–19	ECG_ventSys_phase (m, p25, p75, s, e)	Temporal phase of ventricular systole	ms
20–22	ECG_P_duration (m, s, e)	Duration of P wave	ms
23–25	ECG_QRS_duration (m, s, e)	Duration of QRS complex	ms
26–28	ECG_T_duration (m, s, e)	Duration of T wave	ms
29–31	ECG_pr_interval_ms (m, s, e)	PR interval duration	ms
32–35	ECG_pr_segment_ms (m, p25, s, e)	PR segment duration	ms
36–37	ECG_st_interval_ms (s, e)	ST interval variability	ms
38–40	ECG_st_segment_ms (m, s, e)	ST segment duration	ms
41–44	ECG_qt_interval_ms (m, p75, s, e)	QT interval duration	ms
45	ECG_ecgBeatCenterFreq	Center frequency of ECG beat morphology	Hz
46–48	ECG_ecgInterbeat_eigval1–3	Inter-beat ECG morphology eigenvalues	unitless

Supplemental Table E2. Summary of selected HRV-based physiomarkers after the preprocessing step in our study. Abbreviations – F.N.: feature number; Summary statistics: m = mean; p25 = 25th percentile; p75 = 75th percentile; s = skewness; e = entropy.

F.N.	Selected Base Feature	Description	Unit
49	HRV_rqa_REC	Recurrence rate (RQA)	unitless
50	HRV_rqa_DET	Determinism (RQA)	unitless
51	HRV_rqa_LAM	Laminarity (RQA)	unitless
52	HRV_SDNN	Global NN variability	ms
53	HRV_SDANN1	Long-term HRV (1-min)	ms
54	HRV_SDNNI1	Short-term HRV (1-min)	ms
55	HRV_MadNN	Robust NN dispersion	ms
56	HRV_MCVNN	Median coefficient of variation	%
57	HRV_IQRNN	Interquartile NN variability	ms
58	HRV_SDRMSSD	Long-/short-term variability ratio	unitless
59	HRV_Prc80NN	Upper-tail NN percentile	ms
60	HRV_pNN50	High-frequency variability	%
61–62	HRV_MinNN / MaxNN	Extreme NN intervals	ms
63	HRV_HTI	HRV triangular index	unitless
64	HRV_TINN	NN histogram width	ms
65–68	HRV_VLF / LF / HF / VHF	Spectral HRV power bands	ms^2
69	HRV_TP	Total spectral power	ms^2
70	HRV_LFHF	Sympathovagal balance	unitless
71–72	HRV_LFn / HFn	Normalized spectral power	%

F.N.	Selected Base Feature	Description	Unit
73	HRV_LnHF	Log HF power	unitless
74	HRV_SD1SD2	Poincaré variability ratio	unitless
75	HRV_S	Poincaré ellipse area	ms²
76	HRV_CVI	Cardiac vagal index	unitless
77	HRV_PIP	Phase-rectified index	unitless
78–79	HRV_PSS / PAS	Spectral slope and asymmetry	unitless
80	HRV_GI	Gini index of NN	unitless
81–83	HRV_SI / AI / PI	Nonlinear symmetry indices	unitless
84–86	HRV_C1d / C2d / Cd	Chaos-based indices	unitless
87–88	HRV_DFA_alpha1 / alpha2	Scaling exponents	unitless
89–95	HRV_MFDFA_alpha1_*	Multifractal short-term descriptors	unitless
96–103	HRV_MFDFA_alpha2_*	Multifractal long-term descriptors	unitless
104–107	HRV_ApEn / SampEn / ShanEn / FuzzyEn	Entropy measures	unitless
108–109	HRV_MSEn / CMSEn	Multiscale entropy	unitless
110–113	HRV_CD / HFD / KFD / LZC	Fractal & symbolic complexity	unitless

Supplemental Table E3. Summary of selected PPG-derived physiomarkers after the preprocessing step in our study. Abbreviations – F.N.: feature number; Summary statistics: m = mean; p25 = 25th percentile; p75 = 75th percentile; s = skewness; e = entropy.

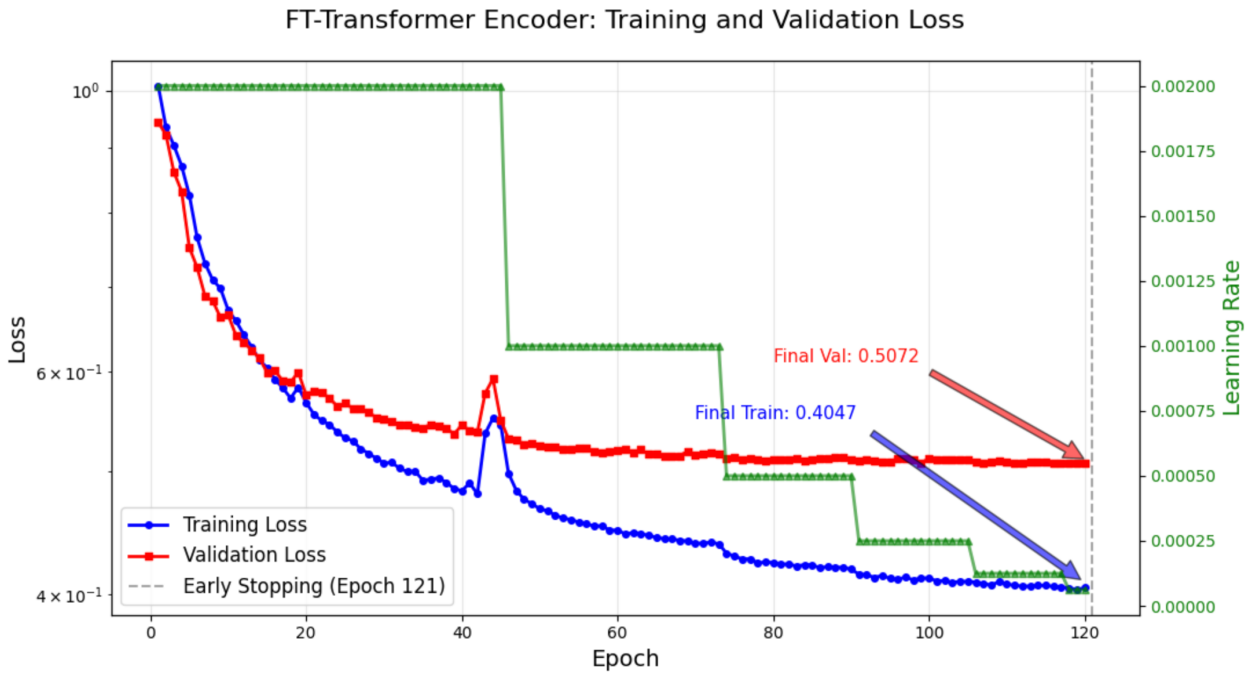
F.N.	Selected Base Feature (stats)	Description	Unit
114–117	PPG_AUC_pulse_nu (m, p25, s, e)	Area under full pulse	normalized
118	PPG_AUC_sys_nu (e)	Systolic AUC complexity	normalized
119–120	PPG_AUC_dias_nu (m, e)	Diastolic AUC	normalized
121–123	PPG_AUCow_nu (m, s, e)	Onset-to-peak AUC	normalized
124–127	PPG_AUCwo_nu (m, p25, s, e)	Peak-to-offset AUC	normalized
128–131	PPG_AUCos_nu (m, p25, s, e)	Onset-to-shoulder AUC	normalized
132–136	PPG_AUCso_nu (m, p25, p75, s, e)	Shoulder-to-offset AUC	normalized
137–138	PPG_Tsys_ms (m, e)	Systolic duration	ms
139–140	PPG_Tdias_ms (m, e)	Diastolic duration	ms
141–144	PPG_T_ow_ms (m, p25, s, e)	Onset-to-peak time	ms
145–146	PPG_T_wo_ms (s, e)	Peak-to-offset time	ms
147–149	PPG_T_os_ms (m, s, e)	Onset-to-shoulder time	ms
150–151	PPG_T_so_ms (s, e)	Shoulder-to-offset time	ms
152–153	PPG_T_so_cd_ms (s, e)	Shoulder-to-dicrotic notch	ms
154–158	PPG_A_AC (m, p25, p75, s, e)	Pulsatile amplitude	a.u.
159–163	PPG_A_off (m, p25, p75, s, e)	Offset amplitude	a.u.
164–166	PPG_A_sp (m, s, e)	Systolic peak amplitude	a.u.
167–169	PPG_A_dn (m, s, e)	Dicrotic notch amplitude	a.u.
170–172	PPG_mean_slope_os (m, s, e)	Mean upstroke slope	a.u.
173–175	PPG_mean_slope_so (m, s, e)	Mean downstroke slope	a.u.
176–177	PPG_Delta_T_sd (m, e)	Systolic–diastolic timing	ms
178–180	PPG_RI (m, s, e)	Reflection index	unitless

F.N.	Selected Base Feature (stats)	Description	Unit
181–183	PPG_SI (m, s, e)	Stiffness index	unitless
184–188	PPG_Delta_A_dn_dp (m, p25, p75, s, e)	DN–DP amplitude difference	a.u.
189–191	PPG_T_dn_dp_ms (m, s, e)	DN–DP timing difference	ms
192–194	PPG_max_upslope (m, s, e)	Max upstroke slope	a.u.
195–199	PPG_pat_ms (m, p25, p75, s, e)	Pulse arrival time	ms
200–204	PPG_dpat_ms (m, p25, p75, s, e)	PAT temporal change	ms/s
205–208	PPG_Delta_A_sp_sp (m, p25, s, e)	Systolic amplitude change	a.u.
209–210	PPG_Augmentation_index (p25, e)	Arterial augmentation index	%
211–212	PPG_center_freq_ppg_Hz (s, e)	Spectral center frequency	Hz
213–215	PPG_mean_ppg (m, s, e)	Mean PPG pulse	a.u.
216–217	PPG_variance_ppg (s, e)	Pulse variance	a.u.
218–220	PPG_skewness_ppg (m, s, e)	Distribution asymmetry	unitless
221–224	PPG_kurtosis_ppg (m, p25, s, e)	Distribution peakedness	unitless
225–227	PPG_entropy_ppg (m, s, e)	Pulse entropy	unitless
228–229	PPG_energy_ppg (s, e)	Pulse energy	a.u.
230–241	PPG_PW_10/25/33/50/66/75 (s, e)	Pulse width metrics	ms
242	PPG_ppgBeatCenterFreq	Dominant beat frequency	Hz
243–245	PPG_ppgInterbeat_eigval1–3	Inter-beat eigenvalues	unitless
246	PPG_Ton_off_ms (s)	Onset-to-offset pulse width	ms
247–248	PPG_Tsp_sp_ms (s, e)	Peak-to-peak interval between systolic peaks	ms
249	PPG_PR (s)	Pulse rate variability derived from PPG	ms

Supplemental Table E4. Summary of selected RESP-derived physiomarkers and physiologic covariates after the preprocessing step in our study. Abbreviations – F.N.: feature number; Summary statistics: m = mean; p25 = 25th percentile; p75 = 75th percentile; s = skewness; e = entropy.

F.N.	Selected Base Feature (stats)	Description	Unit
250–253	RESP_insp_time (m, p25, s, e)	Inspiration duration	s
254–257	RESP_exp_time (m, p25, s, e)	Expiration duration	s
258–262	RESP_insp_exp_ratio (m, p25, p75, s, e)	I:E ratio	unitless
263–266	RESP_resp_width_PPresp_s (m, p25, s, e)	Respiratory cycle width	s
267–268	RESP_resp_rate_Bpm (s, e)	Respiratory rate variability	breaths/min
269	Binary_sbp	Hypotension criterion (SBP ≤100 mmHg)	unitless (0/1)
270	Binary_rr	Tachypnea criterion (RR ≥22 breaths/min)	unitless (0/1)
271	Binary_gcs	Altered mentation criterion (GCS <15)	unitless (0/1)
272	Composite_total	Composite score related to sbp, rr, gcs	unitless (0/1/2/3)

Supplemental Figure E1:



Supplemental Section E1.

Data Representation or Transformation Techniques for Comparison

1. No Transformation: Raw standardized features after pre-processing (272 dimensions) were used directly without dimensionality reduction, serving as a baseline for comparison.

2. Principal Component Analysis (PCA): Linear dimensionality reduction retained principal components of features explaining 90% of cumulative variance in the data†.

3. Deep Variational Autoencoder (DVAE): The DVAE employed a symmetric fully connected architecture for unsupervised nonlinear representation learning. The encoder network compressed 272-dimensional inputs through two progressively narrower dense layers (256→128 units) with ReLU activations, batch normalization (momentum=0.99), and dropout regularization (rate=0.1). The encoder produced two 32-dimensional outputs: mean (μ) and log-variance (log σ^2) vectors parameterizing the latent distribution.

Using the reparameterization trick‡, latent samples were drawn as: $z = \mu + \sigma \odot \varepsilon$, where $\varepsilon \sim N(0, I)$, ensuring differentiability for backpropagation. The decoder mirrored the encoder architecture (128→256 units) to reconstruct the original 272-dimensional feature space from 32-dimensional latent embeddings. Training minimized a composite loss function:

$$L = MSE(x, \hat{x}) + \beta \cdot KL(\, q(z|x) \,||\, p(z)\,)$$

where MSE represents mean squared reconstruction error, KL denotes Kullback-Leibler divergence between the learned posterior q(z|x) and prior p(z)=N(0,I), and SP-2 is a weighting coefficient fixed to 1 throughout training. This β-VAE formulation encouraged learning disentangled, interpretable latent representations*.

Optimization used the Adam optimizer (learning rate=0.001) with ReduceLROnPlateau scheduling (patience ≈ 6, factor = 0.5) and early stopping (patience=20, monitoring validation loss). Training ran for a maximum of 200 epochs with a batch size of 32 and a 90/10 train-validation split. The resulting 32-dimensional DVAE embeddings captured nonlinear physiological relationships while preserving critical information for downstream clustering. All architectural and optimization parameters were selected to ensure stable training on high-dimensional tabular data.

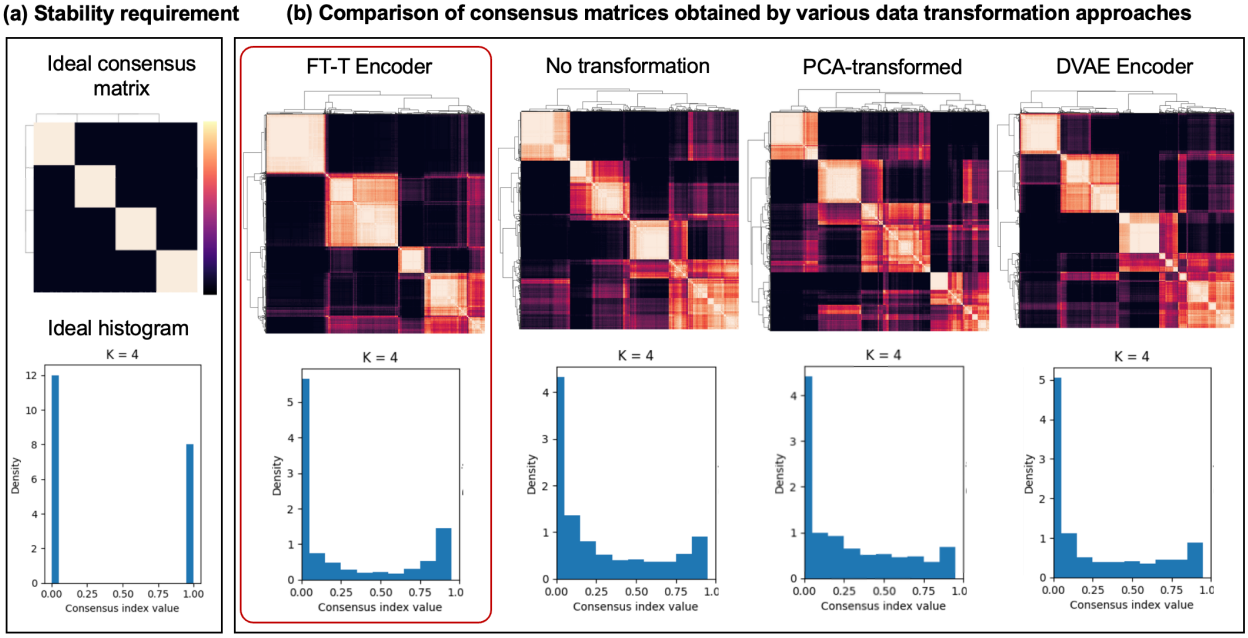
REFERENCE:

†: Jolliffe, I. T. & Cadima, J. Principal component analysis: a review and recent developments. *Philos. Trans. R. Soc. Math. Phys. Eng. Sci.* **374**, 20150202 (2016).

‡: Kingma, D. P. & Welling, M. Auto-Encoding Variational Bayes. Preprint at https://doi.org/10.48550/arXiv.1312.6114 (2022).

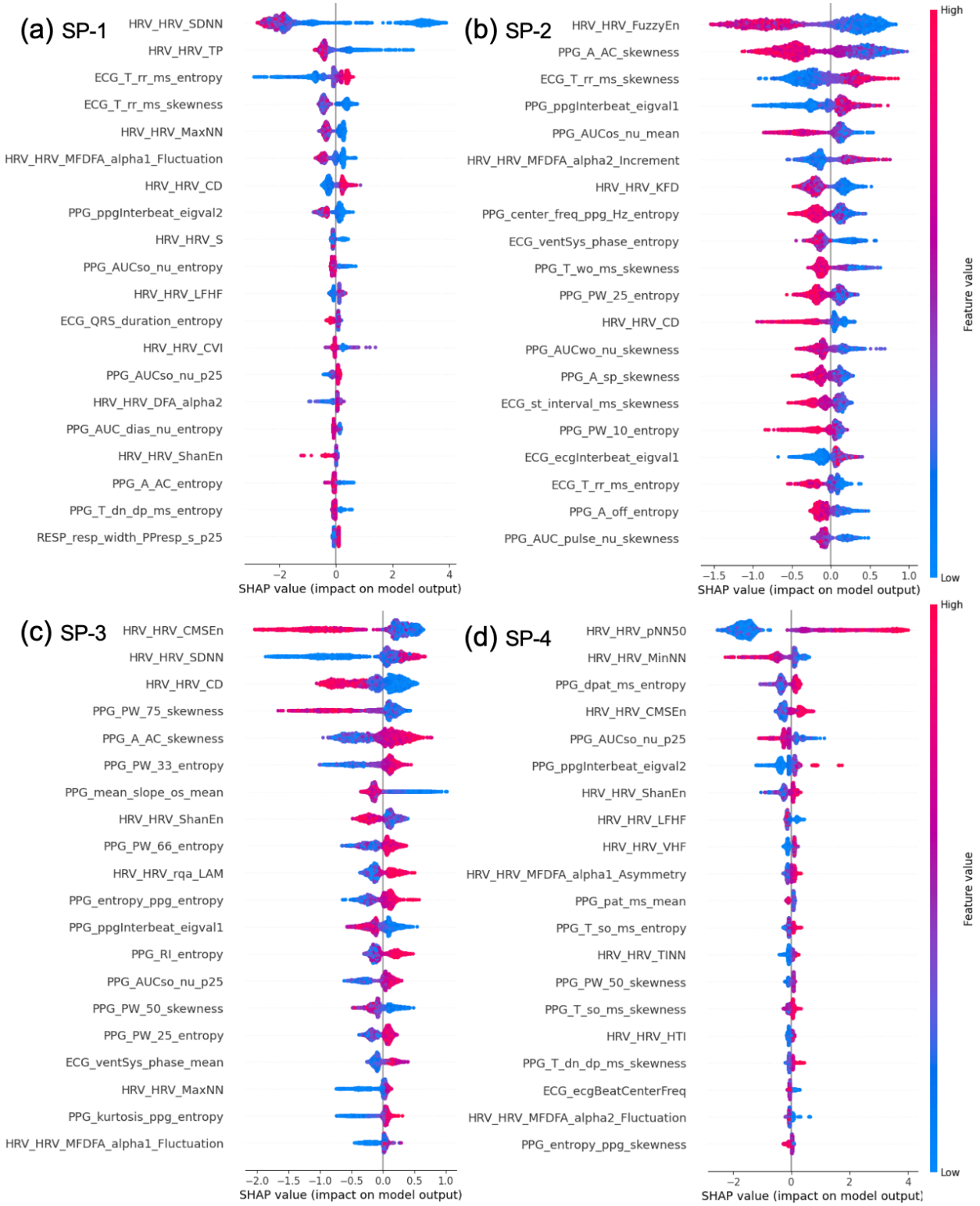
*: Higgins, I. *et al.* beta-VAE: Learning Basic Visual Concepts with a Constrained Variational Framework. *ICLR* (2017).

Supplemental Figure E2.

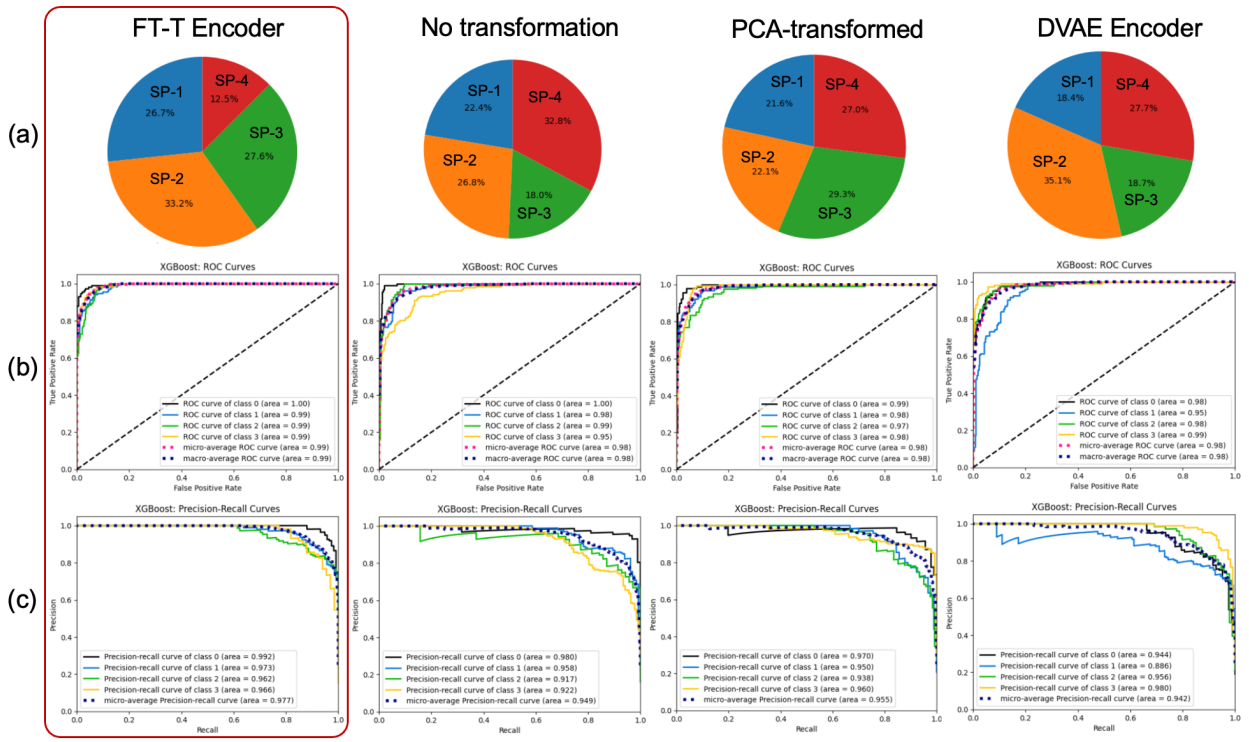


Supplemental Figure E3.

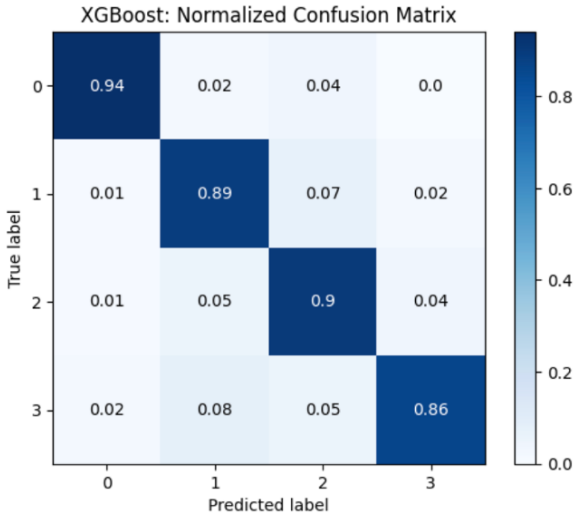
Supplemental Figure E4.



Supplemental Figure E5.



Supplemental Figure E6.



(a)

Train-test portion: randomized 80-20%

Metric	SP-1	SP-2	SP-3	SP-4
Precision	0.965	0.904	0.851	0.891
Recall	0.94	0.891	0.904	0.864
F1-score	0.952	0.898	0.877	0.877
Accuracy	0.94	0.891	0.904	0.864

(b)

Supplemental Table E5. Baseline comorbidity analysis with the Charlson Comorbidity Index (CCI) based on all ICD-10 diagnosis codes prior to the zero-point of our study.

Variable	Overall	SP-1	SP-2	SP-3	SP-4	p-value
Myocardial infarction	375 (17.4%)	97 (16.8%)	111 (15.4%)	100 (16.8%)	67 (24.7%)	0.010
Congestive heart failure	568 (26.3%)	121 (21.0%)	179 (24.9%)	143 (24.1%)	125 (46.1%)	0.000
Peripheral vascular disease	282 (13.0%)	69 (12.0%)	77 (10.7%)	83 (14.0%)	53 (19.6%)	0.003
Cerebrovascular disease	335 (15.5%)	91 (15.8%)	96 (13.4%)	103 (17.3%)	45 (16.6%)	0.221
Dementia	108 (5.0%)	20 (3.5%)	41 (5.7%)	20 (3.4%)	27 (10.0%)	0.000
Chronic pulmonary disease	726 (33.6%)	177 (30.7%)	258 (35.9%)	183 (30.8%)	108 (39.9%)	0.014
Rheumatologic disease	91 (4.2%)	26 (4.5%)	31 (4.3%)	29 (4.9%)	5 (1.8%)	0.139
Peptic ulcer disease	119 (5.5%)	26 (4.5%)	40 (5.6%)	40 (6.7%)	13 (4.8%)	0.381
Mild liver disease	327 (15.1%)	89 (15.4%)	114 (15.9%)	90 (15.2%)	34 (12.5%)	0.612
Diabetes	821 (38.0%)	214 (37.1%)	272 (37.8%)	203 (34.2%)	132 (48.7%)	0.001
Diabetes with complications	335 (15.5%)	81 (14.0%)	103 (14.3%)	84 (14.1%)	67 (24.7%)	0.000
Hemiplegia/paraplegia	129 (6.0%)	31 (5.4%)	41 (5.7%)	45 (7.6%)	12 (4.4%)	0.235
Renal disease	626 (29.0%)	149 (25.8%)	199 (27.7%)	164 (27.6%)	114 (42.1%)	0.000
Any malignancy	67 (3.1%)	21 (3.6%)	20 (2.8%)	17 (2.9%)	9 (3.3%)	0.816
Moderate/severe liver disease	253 (11.7%)	70 (12.1%)	93 (12.9%)	65 (10.9%)	25 (9.2%)	0.364
Metastatic solid tumor	79 (3.7%)	20 (3.5%)	24 (3.3%)	23 (3.9%)	12 (4.4%)	0.854
HIV/AIDS	11 (0.5%)	1 (0.2%)	3 (0.4%)	6 (1.0%)	1 (0.4%)	0.235
Charlson Comorbidity Index	3 (1, 5)	2 (1, 5)	3 (1, 4)	3 (1, 4)	4 (2, 6)	0.000
Age-adjusted Charlson Comorbidity Index	5.0 (3.0, 7.0)	4.0 (2.0, 6.0)	4.0 (2.0, 6.5)	5.0 (2.0, 7.0)	7.0 (5.0, 9.0)	0.000

Supplemental Table E6. Lab values after sepsis-3 onset up to 24 hours in mean (standard deviation) format.

	Overall	SP-1	SP-2	SP-3	SP-4	P-Value	Test
n	2152	575	713	593	271		
Albumin_avg_24h_post, mean (SD)	2.950 (0.577)	2.928 (0.580)	2.976 (0.565)	2.930 (0.580)	2.972 (0.597)	0.609	One-way ANOVA
AlkPhos_avg_24h_post, mean (SD)	106.047 (120.474)	111.790 (163.265)	107.076 (111.378)	97.306 (74.168)	111.185 (120.764)	0.437	One-way ANOVA
ALT_avg_24h_post, mean (SD)	119.097 (423.918)	135.862 (442.246)	98.264 (387.101)	128.291 (413.561)	117.730 (501.068)	0.666	One-way ANOVA
ArterialPh_avg_24h_post, mean (SD)	7.354 (0.079)	7.346 (0.076)	7.361 (0.077)	7.351 (0.086)	7.364 (0.077)	0.103	One-way ANOVA
AST_avg_24h_post, mean (SD)	184.216 (667.374)	228.506 (755.703)	131.339 (440.724)	202.652 (743.596)	188.673 (781.546)	0.254	One-way ANOVA
BaseDeficitArterial_avg_24h_post, mean (SD)	4.893 (3.884)	5.005 (3.563)	4.663 (3.773)	5.135 (4.334)	4.432 (3.487)	0.453	One-way ANOVA
Bicarb_avg_24h_post, mean (SD)	23.709 (5.458)	23.306 (5.189)	24.220 (5.589)	23.058 (5.273)	24.662 (5.827)	<0.001	One-way ANOVA
BNP_avg_24h_post, mean (SD)	637.323 (823.672)	522.625 (703.562)	540.449 (861.061)	697.763 (696.109)	930.515 (991.443)	0.098	One-way ANOVA
BUN_avg_24h_post, mean (SD)	31.752 (25.279)	31.996 (25.389)	30.035 (22.936)	31.369 (27.665)	36.621 (24.950)	0.009	One-way ANOVA
Calcium_avg_24h_post, mean (SD)	9.125 (0.733)	9.052 (0.647)	9.167 (0.716)	9.068 (0.769)	9.302 (0.837)	0.055	One-way ANOVA
Chloride_avg_24h_post, mean (SD)	103.479 (6.792)	103.095 (6.595)	103.240 (6.901)	104.216 (6.759)	103.268 (6.903)	0.034	One-way ANOVA
Creatinine_avg_24h_post, mean (SD)	1.800 (1.906)	1.874 (1.883)	1.728 (1.836)	1.851 (2.185)	1.723 (1.402)	0.504	One-way ANOVA
Glucose_avg_24h_post, mean (SD)	146.721 (58.411)	150.366 (62.099)	146.814 (59.371)	145.430 (56.918)	141.620 (50.323)	0.271	One-way ANOVA
Hgb_avg_24h_post, mean (SD)	10.567 (2.242)	10.643 (2.271)	10.657 (2.310)	10.480 (2.194)	10.369 (2.100)	0.246	One-way ANOVA
iCal_avg_24h_post, mean (SD)	1.132 (0.113)	1.129 (0.114)	1.150 (0.112)	1.118 (0.115)	1.128 (0.107)	0.063	One-way ANOVA
INR_avg_24h_post, mean (SD)	1.714 (1.176)	1.757 (1.151)	1.609 (1.002)	1.699 (1.247)	1.915 (1.403)	0.051	One-way ANOVA
PT_avg_24h_post, mean (SD)	18.972 (7.895)	19.299 (7.921)	17.981 (5.577)	18.736 (8.204)	21.245 (10.867)	<0.001	One-way ANOVA
Lactate_avg_24h_post, mean (SD)	2.330 (2.379)	2.343 (2.128)	2.083 (1.775)	2.631 (3.124)	2.230 (2.198)	0.016	One-way ANOVA
Neut_perc_avg_24h_post, mean (SD)	79.449 (12.753)	80.003 (12.155)	79.278 (11.988)	79.124 (13.356)	79.470 (14.382)	0.762	One-way ANOVA
PaO2_avg_24h_post, mean (SD)	143.634 (70.466)	139.627 (65.273)	134.224 (68.008)	158.989 (74.373)	137.994 (72.588)	<0.001	One-way ANOVA
Platelets_avg_24h_post, mean (SD)	202.809 (109.627)	208.823 (110.782)	194.695 (98.083)	211.616 (119.902)	192.192 (110.506)	0.017	One-way ANOVA
PTT_avg_24h_post, mean (SD)	39.298 (19.715)	40.174 (23.777)	39.047 (18.665)	37.766 (17.708)	42.448 (18.717)	0.300	One-way ANOVA
Sodium_avg_24h_post, mean (SD)	137.435 (5.743)	136.956 (5.442)	137.405 (5.836)	137.730 (5.802)	137.864 (5.938)	0.109	One-way ANOVA
Bilirubin_total_avg_24h_post, mean (SD)	2.108 (4.568)	2.178 (5.022)	2.481 (5.334)	1.782 (3.660)	1.667 (2.570)	0.131	One-way ANOVA
Troponin_avg_24h_post, mean (SD)	81.969 (709.626)	131.418 (1146.434)	119.671 (553.772)	17.574 (59.642)	38.283 (238.335)	0.582	One-way ANOVA
WBC_avg_24h_post, mean (SD)	12.769 (7.353)	13.933 (8.360)	11.898 (6.524)	12.740 (7.115)	12.704 (7.409)	<0.001	One-way ANOVA
Potassium_avg_24h_post, mean (SD)	4.109 (0.637)	4.148 (0.661)	4.079 (0.639)	4.098 (0.648)	4.128 (0.553)	0.318	One-way ANOVA

Supplemental Section E2. Domain-specific prompt supplied to the LLM-based PIA agent for phenotype interpretation and generating a concise clinical report.

E2.1: Main domain-specific prompt and system message used for the LLM-based interpretation.

```
prompt = f"""
Analyze this sepsis physiophenotype based on physiological monitoring data collected 5 minutes
prior to sepsis-3 onset and interpret its physiological state based on sepsis pathophysiology:

CLUSTER DEMOGRAPHICS:
- Number of patients: {n_patients}
- Percentage of cohort: {percentage:.1f}%

TOP DISCRIMINATIVE PHYSIOLOGICAL FEATURES WITH CLINICAL CONTEXT:
{feature_summary}

PHYSIOLOGICAL SYSTEM CONTEXT:
- ECG features: Reflect cardiac electrical activity, systole phases, rhythm, QT prolongation,
T-wave abnormalities and AF
```

- HRV features: Indicate autonomic nervous system function and stress response (e.g., ↓ Lower HRV metrics often indicate dysfunction/stress)
- PPG features: Show peripheral circulation, perfusion and arterial stiffness
- Respiratory features: Indicate breathing patterns and respiratory mechanics
- qSOFA features: Clinical proxy for organ dysfunction risk in sepsis (SBP ≤ 100, RR ≥ 22, altered mentation)

SEPSIS PATHOPHYSIOLOGY CONSIDERATIONS:
- Autonomic dysfunction is common in sepsis (e.g., ↓ Lower HRV patterns like SDNN, HF power, Complexity measures (S, ShanEn, CD), and DFA alpha indicate impaired autonomic regulation and stress).
- Cardiovascular compromise includes sepsis-induced cardiomyopathy and impaired contractility (ECG features like QT dynamics, QRS changes, arrhythmias).
- Hemodynamic instability & vasodilation come with reduced vascular tone and distributive shock (PPG AC amplitude, pulse arrival time, qSOFA_sbp, SBP).
- Respiratory dysfunction ranges from compensatory tachypnea to respiratory failure and ARDS (respiratory rate, qSOFA_rr).
- Vascular & microcirculatory collapse leads to impaired oxygen delivery and poor tissue perfusion (PPG waveform morphology).
- Systemic inflammation affects all physiological systems, contributing to multi-organ dysfunction (qSOFA).
- Compensated autonomic perturbation is an early or stable state of physiological stress, in which the body maintains vital signs within near-normal ranges (e.g., qSOFA = 0) despite underlying autonomic nervous system imbalance (e.g., tachycardia, altered HRV LF/HF ratio, mild tachypnea).

IMPORTANT INTERPRETATION GUIDELINES:
- Pay close attention to whether each feature value is "↑ Higher" or "↓ Lower" relative to the overall cohort.
- Use the specific "Clinical meaning" provided for each feature to understand the physiological implication of its change.
- For example, if HRV_HRV_SDNN is "↓ Lower values (High importance...)", interpret this as reduced overall HRV and autonomic balance, indicating dysfunction.
- Similarly, if PPG_A_sp_mean is "↑ Higher values", interpret this as higher average systolic pulse amplitude, which might indicate changes in peripheral perfusion or arterial tone depending on the context.

Based on these discriminative physiological patterns (directions and specific clinical meanings), please provide:

1. PHENOTYPE NAME: A clinically meaningful title (4-6 words) that captures the DISTINCTIVE pathophysiological pattern of THIS specific cluster. Focus on the specific combination of HIGH/LOW features mentioned in the 'TOP DISCRIMINATIVE PHYSIOLOGICAL FEATURES' section. For example, if the top features are predominantly ↓ Lower HRV Complexity (S, FuzzyEn) and ↑ Higher PPG Amplitude (A_AC), the name might be 'Reduced Complexity with Enhanced Pulse Strength'. If top features are ↑ Higher pNN50 (parasympathetic tone) and ↑ Higher HRV_ShanEn

```
(complexity), it might be 'Enhanced Parasympathetic Complexity'. Avoid generic terms like
"Dysfunction" or "Compromise" if the specific features suggest a more nuanced state.

2. PATHOPHYSIOLOGICAL INTERPRETATION:
    - What specific sepsis mechanisms does this pattern of HIGHER/LOWER features suggest?
Focus on the specific metrics mentioned.
    - Which organ systems appear most affected based on the specific features and their
changes?
    - What does the specific autonomic function pattern (based on detailed HRV metrics)
indicate?

3. CLINICAL CHARACTERISTICS:
    - What would patients in this phenotype likely present with clinically, based on the
specific feature changes?
    - What hemodynamic profile would be expected?
    - What respiratory patterns might be observed?

Format your response with clear section headers and focus on the clinical significance of the
specific physiological patterns and their directions.
"""

messages=[
{"role": "system", "content": "You are an expert clinical data scientist
specializing in sepsis pathophysiology and critical care medicine."},
{"role": "user", "content": prompt}
]
```

E2.2: Detailed clinical contexts of physiomarkers or physiological features, useful to generate feature_summary lines for the SHAP-identified important features.

```
feature_contexts = {
# ECG Features
'T_rr_ms': 'RR interval (successive R-peaks interval) - reflects heart rhythm regularity',
'HR_bpm': 'Heart Rate - primary cardiac vital sign',
'edr_rate_Bpm': 'Respiratory rate estimated from ECG - cardiorespiratory coupling',
'atrialSys_phase': 'Phase of atrial systole - atrial contraction timing',
'ventSys_phase': 'Phase of ventricular systole - ventricular contraction timing',
'P_duration': 'Duration of P wave - atrial depolarization time',
'QRS_duration': 'Duration of QRS complex - ventricular depolarization time',
'T_duration': 'Duration of T wave - ventricular repolarization time',
'pr_interval_ms': 'PR interval - atrioventricular conduction time',
'pr_segment_ms': 'PR segment - atrioventricular conduction segment',
'st_interval_ms': 'ST interval - early ventricular repolarization',
'st_segment_ms': 'ST segment - early ventricular repolarization segment',
'qt_interval_ms': 'QT interval - total ventricular electrical activity',
'qtc_interval_ms': 'Corrected QT interval - heart rate corrected ventricular repolarization',
```

```
'ecgBeatCenterFreq': 'Center frequency of ECG beat - dominant frequency in ECG spectrum',
'ecgInterbeat_eigval1': '1st eigenvalue of interbeat ECG covariance matrix - dominant
interbeat ECG mode',
'ecgInterbeat_eigval2': '2nd eigenvalue of interbeat ECG covariance matrix - secondary
interbeat ECG mode',
'ecgInterbeat_eigval3': '3rd eigenvalue of interbeat ECG covariance matrix - tertiary
interbeat ECG mode',

# HRV Features - RQA
'rqa_REC': 'Recurrence rate from RQA of HRV - probability of repeated states (HRV pattern
repetition)',
'rqa_DET': 'Determinism from RQA of HRV - predictability of HRV patterns',
'rqa_LAM': 'Laminarity from RQA of HRV - presence of laminar phases in HRV dynamics',

# HRV Features - Time Domain
'HRV_MeanNN': 'Mean of NN intervals - average heart rhythm',
'HRV_SDNN': 'Standard deviation of NN intervals - overall HRV, autonomic balance',
'HRV_SDANN1': 'SD of 1-min averages of NN intervals - long-term HRV variability',
'HRV_SDNNI1': 'Mean of 1-min SD of NN intervals - short-term HRV variability',
'HRV_SDANN2': 'SD of 2-min averages of NN intervals - intermediate-term HRV variability',
'HRV_SDNNI2': 'Mean of 2-min SD of NN intervals - short-term HRV variability',
'HRV_SDANN5': 'SD of 5-min averages of NN intervals - intermediate-term HRV variability',
'HRV_SDNNI5': 'Mean of 5-min SD of NN intervals - short-term HRV variability',
'HRV_RMSSD': 'Root mean square of successive differences - short-term HRV, parasympathetic
activity',
'HRV_SDSD': 'SD of successive differences - short-term HRV variability',
'HRV_CVNN': 'Coefficient of variation of NN intervals - normalized HRV',
'HRV_CVSD': 'Coefficient of variation of successive differences - normalized short-term HRV',
'HRV_MedianNN': 'Median of NN intervals - median heart rhythm',
'HRV_MadNN': 'Median absolute deviation of NN intervals - robust measure of HRV dispersion',
'HRV_MCVNN': 'Median-based coefficient of variation - normalized HRV based on median',
'HRV_IQRNN': 'Interquartile range of NN intervals - robust measure of HRV range',
'HRV_SDRMSSD': 'Ratio of SDNN to RMSSD - balance between long and short-term variability',
'HRV_Prc20NN': '20th percentile of NN intervals - lower range of heart rhythm',
'HRV_Prc80NN': '80th percentile of NN intervals - upper range of heart rhythm',
'HRV_pNN50': 'Proportion of NN intervals differing by >50ms - parasympathetic tone',
'HRV_pNN20': 'Proportion of NN intervals differing by >20ms - short-term HRV',
'HRV_MinNN': 'Minimum of NN intervals - shortest R-R interval',
'HRV_MaxNN': 'Maximum of NN intervals - longest R-R interval',
'HRV_HTI': 'HRV triangular index - geometric measure of HRV',
'HRV_TINN': 'Triangular interpolation of NN histogram - HRV distribution width',

# HRV Features - Frequency Domain
'HRV_ULF': 'Power in ultra-low frequency band (<0.003 Hz) - long-term regulation',
'HRV_VLF': 'Power in very low frequency band (0.003-0.04 Hz) - thermoregulation, slow
mechanisms',
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'HRV_LF': 'Power in low frequency band (0.04–0.15 Hz) – sympathetic and parasympathetic activity',
'HRV_HF': 'Power in high frequency band (0.15–0.4 Hz) – parasympathetic activity, respiratory sinus arrhythmia',
'HRV_VHF': 'Power in very high frequency band (>0.4 Hz) – very rapid HRV components',
'HRV_TP': 'Total power – overall autonomic activity',
'HRV_LFHF': 'Ratio of LF to HF – sympathovagal balance',
'HRV_LFn': 'Normalized low frequency power – % of LF in total power',
'HRV_HFn': 'Normalized high frequency power – % of HF in total power',
'HRV_LnHF': 'Natural log of HF power – log-transformed parasympathetic activity',

# HRV Features – Poincaré Plot
'HRV_SD1': 'Poincaré plot SD1 – short-term variability, parasympathetic activity',
'HRV_SD2': 'Poincaré plot SD2 – long-term variability, sympathetic activity',
'HRV_SD1SD2': 'Ratio SD1/SD2 – balance between short and long-term variability',
'HRV_S': 'Area of Poincaré ellipse – overall HRV scatter area',
'HRV_CSI': 'Cardiac Sympathetic Index – derived from Poincaré plot (SD2/SD1)',
'HRV_CVI': 'Cardiac Vagal Index – derived from Poincaré plot (SD1^2)',
'HRV_CSI_Modified': 'Modified Cardiac Sympathetic Index – alternative sympathovagal balance measure',
'HRV_PIP': 'Phase-rectified signal average index – non-linear HRV pattern measure',
'HRV_IALS': 'Integral of absolute value of successive differences – cumulative HRV change',
'HRV_PSS': 'Power spectral slope – slope of HRV power spectrum',
'HRV_PAS': 'Power spectral asymmetry – asymmetry of HRV power spectrum',
'HRV_GI': 'Gini index of NN interval distribution – inequality measure of HRV distribution',
'HRV_SI': 'Slope index – derived from Poincaré plot',
'HRV_AI': 'Asymmetry index – derived from Poincaré plot',
'HRV_PI': 'Phase index – derived from Poincaré plot',
'HRV_C1d': 'Chaos-based parameter C1d – chaos measure using derivatives',
'HRV_C1a': 'Chaos-based parameter C1a – chaos measure using amplitudes',
'HRV_SD1d': 'Derivative-based SD1 – Poincaré short-term variability (derivative)',
'HRV_SD1a': 'Amplitude-based SD1 – Poincaré short-term variability (amplitude)',
'HRV_C2d': 'Chaos-based parameter C2d – chaos measure using derivatives',
'HRV_C2a': 'Chaos-based parameter C2a – chaos measure using amplitudes',
'HRV_SD2d': 'Derivative-based SD2 – Poincaré long-term variability (derivative)',
'HRV_SD2a': 'Amplitude-based SD2 – Poincaré long-term variability (amplitude)',
'HRV_Cd': 'Chaos index using derivatives – overall chaos measure',
'HRV_Ca': 'Chaos index using amplitudes – overall chaos measure',
'HRV_SDNNd': 'SDNN based on derivative transformation – HRV variability (derivative)',
'HRV_SDNNa': 'SDNN based on amplitude transformation – HRV variability (amplitude)',

# HRV Features – Fractal & Multifractal
'HRV_DFA_alpha1': 'DFA scaling exponent (short-term) – fractal properties (4–16 beats)',
'HRV_MFDFA_alpha1_Width': 'Width of multifractal spectrum (alpha1) – multifractal variability range (short-term)',
'HRV_MFDFA_alpha1_Peak': 'Peak of multifractal spectrum (alpha1) – dominant multifractal scaling (short-term)',
```

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'HRV_MFDFA_alpha1_Mean': 'Mean of multifractal spectrum (alpha1) – average multifractal scaling (short-term)',
'HRV_MFDFA_alpha1_Max': 'Max of multifractal spectrum (alpha1) – maximum multifractal scaling (short-term)',
'HRV_MFDFA_alpha1_Delta': 'Difference (Max – Min) in multifractal alpha1 – multifractal width (short-term)',
'HRV_MFDFA_alpha1_Asymmetry': 'Asymmetry of multifractal alpha1 – skewness of spectrum (short-term)',
'HRV_MFDFA_alpha1_Fluctuation': 'Fluctuation index in multifractal alpha1 – multifractal fluctuation (short-term)',
'HRV_MFDFA_alpha1_Increment': 'Increment of multifractal alpha1 – multifractal change (short-term)',
'HRV_DFA_alpha2': 'DFA scaling exponent (long-term) – fractal properties (16+ beats)',
'HRV_MFDFA_alpha2_Width': 'Width of multifractal spectrum (alpha2) – multifractal variability range (long-term)',
'HRV_MFDFA_alpha2_Peak': 'Peak of multifractal spectrum (alpha2) – dominant multifractal scaling (long-term)',
'HRV_MFDFA_alpha2_Mean': 'Mean of multifractal spectrum (alpha2) – average multifractal scaling (long-term)',
'HRV_MFDFA_alpha2_Max': 'Max of multifractal spectrum (alpha2) – maximum multifractal scaling (long-term)',
'HRV_MFDFA_alpha2_Delta': 'Delta (Max – Min) of alpha2 – multifractal width (long-term)',
'HRV_MFDFA_alpha2_Asymmetry': 'Asymmetry of multifractal alpha2 – skewness of spectrum (long-term)',
'HRV_MFDFA_alpha2_Fluctuation': 'Fluctuation in alpha2 – multifractal fluctuation (long-term)',
'HRV_MFDFA_alpha2_Increment': 'Increment in alpha2 – multifractal change (long-term)',

# HRV Features – Nonlinear
'HRV_ApEn': 'Approximate Entropy – signal regularity and complexity',
'HRV_SampEn': 'Sample Entropy – pattern regularity in heart rhythm',
'HRV_ShanEn': 'Shannon Entropy – measure of HRV signal complexity',
'HRV_FuzzyEn': 'Fuzzy Entropy – measure of HRV signal complexity using fuzzy sets',
'HRV_MSEn': 'Multiscale Entropy (mean of scales) – complexity across multiple time scales',
'HRV_CMSEn': 'Composite Multiscale Entropy – refined multiscale complexity measure',
'HRV_RCMSEn': 'Refined Composite Multiscale Entropy – advanced multiscale complexity measure',
'HRV_CD': 'Correlation Dimension – measure of HRV attractor complexity',
'HRV_HFD': 'Higuchi Fractal Dimension – measure of HRV signal irregularity',
'HRV_KFD': 'Katz Fractal Dimension – measure of HRV signal complexity',
'HRV_LZC': 'Lempel-Ziv Complexity – measure of HRV signal pattern complexity',
'HRV_MSE_0': 'Multiscale Entropy at scale 0 – complexity at finest scale',
'HRV_MSE_1': 'Multiscale Entropy at scale 1 – complexity at scale 1',
'HRV_MSE_2': 'Multiscale Entropy at scale 2 – complexity at scale 2',
'HRV_MSE_3': 'Multiscale Entropy at scale 3 – complexity at scale 3',
'HRV_MSE_4': 'Multiscale Entropy at scale 4 – complexity at scale 4',
'HRV_MSE_5': 'Multiscale Entropy at scale 5 – complexity at scale 5',
'HRV_MSE_6': 'Multiscale Entropy at scale 6 – complexity at scale 6',
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'HRV_MSE_7': 'Multiscale Entropy at scale 7 – complexity at scale 7',
'HRV_MSE_8': 'Multiscale Entropy at scale 8 – complexity at scale 8',
'HRV_MSE_9': 'Multiscale Entropy at scale 9 – complexity at scale 9',
'HRV_MSE_10': 'Multiscale Entropy at scale 10 – complexity at scale 10',
'HRV_MSE_11': 'Multiscale Entropy at scale 11 – complexity at scale 11',
'HRV_MSE_12': 'Multiscale Entropy at scale 12 – complexity at scale 12',
'HRV_MSE_13': 'Multiscale Entropy at scale 13 – complexity at scale 13',
'HRV_MSE_14': 'Multiscale Entropy at scale 14 – complexity at scale 14',
'HRV_MSE_15': 'Multiscale Entropy at scale 15 – complexity at scale 15',
'HRV_MSE_16': 'Multiscale Entropy at scale 16 – complexity at scale 16',
'HRV_MSE_17': 'Multiscale Entropy at scale 17 – complexity at scale 17',
'HRV_MSE_18': 'Multiscale Entropy at scale 18 – complexity at scale 18',
'HRV_MSE_19': 'Multiscale Entropy at scale 19 – complexity at scale 19',

# PPG Features – Waveform
'PPG_AUC_pulse_nu': 'Area under pulse wave (normalized) – stroke volume surrogate',
'PPG_AUC_sys_nu': 'Area under systolic part (normalized) – systolic blood flow',
'PPG_AUC_dias_nu': 'Area under diastolic part (normalized) – diastolic filling',
'PPG_IPA': 'Inflection point area – arterial stiffness indicator',
'PPG_AUCow_nu': 'AUC onset to wave peak (normalized) – early systolic area',
'PPG_AUCwo_nu': 'AUC wave peak to offset (normalized) – late systolic + diastolic area',
'PPG_AUCos_nu': 'AUC onset to shoulder (normalized) – early systolic + shoulder area',
'PPG_AUCso_nu': 'AUC shoulder to offset (normalized) – shoulder to diastolic area',
'PPG_Tsys_ms': 'Duration of systolic phase – left ventricular ejection time',
'PPG_Tdias_ms': 'Duration of diastolic phase – filling time',
'PPG_T_ow_ms': 'Onset to wave peak time – systolic rise time',
'PPG_T_wo_ms': 'Wave peak to offset time – systolic + early diastolic time',
'PPG_T_os_ms': 'Onset to shoulder time – systolic + shoulder time',
'PPG_T_so_ms': 'Shoulder to offset time – shoulder to early diastolic time',
'PPG_T_so_cd_ms': 'Shoulder to dicrotic notch (or centroid) – dicrotic notch timing',
'PPG_A_AC': 'Amplitude of AC (pulsatile) component – pulse strength',
'PPG_A_off': 'Amplitude at offset – pulse baseline',
'PPG_A_sp': 'Amplitude at shoulder peak – shoulder amplitude',
'PPG_DN_exists': 'Dicrotic notch exists (binary) – presence of dicrotic notch',
'PPG_A_dn': 'Amplitude at dicrotic notch – dicrotic notch amplitude',
'PPG_Ton_off_ms': 'Onset to offset time – total pulse duration',
'PPG_Tsp_sp_ms': 'Shoulder peak to shoulder peak interval – pulse rate indicator',
'PPG_PR': 'Pulse rate from PPG – peripheral heart rate',
'PPG_mean_slope_os': 'Mean slope from onset to shoulder – early systolic upstroke',
'PPG_mean_slope_so': 'Mean slope from shoulder to offset – shoulder to diastolic decay',
'PPG_Delta_T_sd': 'Time difference between systolic and diastolic peak – peak timing diff',
'PPG_RI': 'Reflection Index – arterial stiffness and wave reflection',
'PPG_SI': 'Stiffness Index – large artery stiffness',
'PPG_Delta_A_dn_dp': 'Amplitude diff between dicrotic notch & diastolic peak – dicrotic amp
diff',
'PPG_T_dn_dp_ms': 'Time diff between dicrotic notch & diastolic peak – dicrotic time diff',
'PPG_ppg_class': 'Pulse wave morphology class – categorical shape descriptor',
```

```
'PPG_max_upslope': 'Maximum slope in rising edge – systolic upstroke steepness',
'PPG_pat_ms': 'Pulse arrival time – arterial stiffness and blood pressure',
'PPG_dpat_ms': 'Derivative of PAT over time – change in pulse arrival',
'PPG_Delta_A_sp_sp': 'Amplitude difference between shoulder peaks – shoulder amp variability',
'PPG_Augmentation_index': 'Measure of arterial stiffness – pressure wave augmentation',
'PPG_center_freq_ppg_Hz': 'Center frequency of PPG spectrum – dominant frequency in PPG',
'PPG_mean_ppg': 'Mean of raw PPG signal – average PPG level',
'PPG_median_ppg': 'Median of raw PPG signal – median PPG level',
'PPG_variance_ppg': 'Variance of PPG – PPG signal variability',
'PPG_skewness_ppg': 'Skewness of PPG distribution – PPG signal asymmetry',
'PPG_kurtosis_ppg': 'Kurtosis of PPG distribution – PPG signal peakedness',
'PPG_std_ppg': 'Standard deviation of PPG – PPG signal dispersion',
'PPG_entropy_ppg': 'Entropy of PPG – PPG signal complexity',
'PPG_energy_ppg': 'Energy of PPG signal – total power of PPG',
'PPG_PW_10': 'Pulse width at 10% amplitude – pulse width measure',
'PPG_PW_25': 'Pulse width at 25% amplitude – pulse width measure',
'PPG_PW_33': 'Pulse width at 33% amplitude – pulse width measure',
'PPG_PW_50': 'Pulse width at 50% amplitude – pulse width measure (FWHM)',
'PPG_PW_66': 'Pulse width at 66% amplitude – pulse width measure',
'PPG_PW_75': 'Pulse width at 75% amplitude – pulse width measure',
'PPG_ppgBeatCenterFreq': 'Dominant frequency in PPG beats – dominant frequency in PPG
spectrum',
'PPG_ppgInterbeat_eigval1': '1st eigenvalue of inter-beat PPG matrix – dominant interbeat PPG
mode',
'PPG_ppgInterbeat_eigval2': '2nd eigenvalue of inter-beat PPG matrix – secondary interbeat PPG
mode',
'PPG_ppgInterbeat_eigval3': '3rd eigenvalue of inter-beat PPG matrix – tertiary interbeat PPG
mode',

# Respiratory Features
'RESP_insp_time': 'Inspiration time – respiratory muscle function',
'RESP_exp_time': 'Expiration time – respiratory mechanics',
'RESP_insp_exp_ratio': 'I:E ratio – breathing pattern efficiency',
'RESP_resp_width_PPresp_s': 'Width of P-P respiratory cycle – respiratory period',
'RESP_resp_rate_Bpm': 'Respiratory rate – ventilatory status',

# qSOFA Features
'qSOFA_rr': 'qSOFA respiratory rate score – respiratory dysfunction (score 1 if RR >= 22)',
'qSOFA_sbp': 'qSOFA systolic blood pressure score – hemodynamic instability (score 1 if SBP <=
100 mmHg)',
'qSOFA_gcs': 'qSOFA Glasgow Coma Scale score – neurologic dysfunction (score 1 if GCS < 15)',
'qSOFA_total': 'Total qSOFA score (0-3) – sepsis severity indicator (>=2 suggests higher
risk)'
}
```

E2.3: Summary lines per phenotype to create consolidated feature_summary (fed under the LLM prompt) using the top SHAP features with their directionality information, SHAP values, and feature meanings from feature_contexts table.

Phenotype SP-1:

['1. HRV_HRV_SDNN: ↓ Lower values (High importance, SHAP=2.7727). Clinical meaning: Standard deviation of NN intervals - overall HRV, autonomic balance', '',
'2. HRV_HRV_TP: ↓ Lower values (Low importance, SHAP=0.5337). Clinical meaning: Total power - overall autonomic activity', '',
'3. ECG_T_rr_ms_skewness: ↓ Lower values (Low importance, SHAP=0.3830). Clinical meaning: RR interval (successive R-peaks interval) - reflects heart rhythm regularity', '',
'4. ECG_T_rr_ms_entropy: ↑ Higher values (Low importance, SHAP=0.3819). Clinical meaning: RR interval (successive R-peaks interval) - reflects heart rhythm regularity', '',
'5. HRV_HRV_CVI: ↓ Lower values (Low importance, SHAP=0.2576). Clinical meaning: Cardiac Vagal Index - derived from Poincaré plot (SD1^2)', '',
'6. HRV_HRV_MaxNN: ↓ Lower values (Low importance, SHAP=0.2560). Clinical meaning: Maximum of NN intervals - longest R-R interval', '',
'7. HRV_HRV_MFDFA_alpha1_Fluctuation: ↓ Lower values (Low importance, SHAP=0.2463). Clinical meaning: Fluctuation index in multifractal alpha1 - multifractal fluctuation (short-term)', '',
'8. HRV_HRV_CD: ↑ Higher values (Low importance, SHAP=0.2349). Clinical meaning: Chaos index using derivatives - overall chaos measure', '',
'9. PPG_ppgInterbeat_eigval2: ↓ Lower values (Low importance, SHAP=0.2268). Clinical meaning: 2nd eigenvalue of inter-beat PPG matrix - secondary interbeat PPG mode', '',
'10. HRV_HRV_S: ↓ Lower values (Low importance, SHAP=0.2240). Clinical meaning: Area of Poincaré ellipse - overall HRV scatter area', '']

Phenotype SP-2:

['1. PPG_A_AC_skewness: ↓ Lower values (High importance, SHAP=0.5013). Clinical meaning: Amplitude of AC (pulsatile) component - pulse strength', '',
'2. HRV_HRV_FuzzyEn: ↓ Lower values (High importance, SHAP=0.4908). Clinical meaning: Fuzzy Entropy - measure of HRV signal complexity using fuzzy sets', '',
'3. ECG_T_rr_ms_skewness: ↑ Higher values (Moderate importance, SHAP=0.2892). Clinical meaning: RR interval (successive R-peaks interval) - reflects heart rhythm regularity', '',
'4. HRV_HRV_MFDFA_alpha2_Increment: ↑ Higher values (Moderate importance, SHAP=0.2401). Clinical meaning: Increment in alpha2 - multifractal change (long-term)', '',
'5. PPG_ppgInterbeat_eigval1: ↑ Higher values (Moderate importance, SHAP=0.2070). Clinical meaning: 1st eigenvalue of inter-beat PPG matrix - dominant interbeat PPG mode', '',
'6. PPG_AUCos_nu_mean: ↓ Lower values (Moderate importance, SHAP=0.2045). Clinical meaning: AUC onset to shoulder (normalized) - early systolic + shoulder area', '',
'7. HRV_HRV_KFD: ↓ Lower values (Moderate importance, SHAP=0.1980). Clinical meaning: Katz Fractal Dimension - measure of HRV signal complexity', '',
'8. PPG_T_wo_ms_skewness: ↓ Lower values (Moderate importance, SHAP=0.1789). Clinical meaning: Wave peak to offset time - systolic + early diastolic time', '',
'9. ECG_ventSys_phase_entropy: ↓ Lower values (Moderate importance, SHAP=0.1761). Clinical meaning: Phase of ventricular systole - ventricular contraction timing', '',
'10. PPG_center_freq_ppg_Hz_entropy: ↓ Lower values (Moderate importance, SHAP=0.1689). Clinical meaning: Center frequency of PPG spectrum - dominant frequency in PPG', '']

Phenotype SP-3:
['1. HRV_HRV_CMSEn: ↓ Lower values (High importance, SHAP=0.4897). Clinical meaning: Composite Multiscale Entropy – refined multiscale complexity measure', ’’,
'2. HRV_HRV_SDNN: ↑ Higher values (High importance, SHAP=0.3490). Clinical meaning: Standard deviation of NN intervals – overall HRV, autonomic balance', ’’,
'3. PPG_A_AC_skewness: ↑ Higher values (Moderate importance, SHAP=0.3170). Clinical meaning: Amplitude of AC (pulsatile) component – pulse strength', ’’,
'4. PPG_mean_slope_os_mean: ↓ Lower values (Moderate importance, SHAP=0.2770). Clinical meaning: Mean slope from onset to shoulder – early systolic upstroke', ’’,
'5. HRV_HRV_CD: ↓ Lower values (Moderate importance, SHAP=0.2683). Clinical meaning: Chaos index using derivatives – overall chaos measure', ’’,
'6. PPG_PW_75_skewness: ↓ Lower values (Moderate importance, SHAP=0.2243). Clinical meaning: Pulse width at 75% amplitude – pulse width measure', ’’,
'7. HRV_HRV_ShanEn: ↓ Lower values (Moderate importance, SHAP=0.2045). Clinical meaning: Area of Poincaré ellipse – overall HRV scatter area', ’’,
'8. PPG_ppgInterbeat_eigval1: ↓ Lower values (Moderate importance, SHAP=0.1937). Clinical meaning: 1st eigenvalue of inter-beat PPG matrix – dominant interbeat PPG mode', ’’,
'9. PPG_PW_33_entropy: ↑ Higher values (Moderate importance, SHAP=0.1913). Clinical meaning: Pulse width at 33% amplitude – pulse width measure', ’’,
'10. HRV_HRV_rqa_LAM: ↑ Higher values (Moderate importance, SHAP=0.1828). Clinical meaning: Laminarity from RQA of HRV – presence of laminar phases in HRV dynamics', '']

Phenotype SP-4:
['1. HRV_HRV_pNN50: ↑ Higher values (High importance, SHAP=3.0968). Clinical meaning: Proportion of NN intervals differing by >50ms – parasympathetic tone', ’’,
'2. HRV_HRV_MinNN: ↓ Lower values (Low importance, SHAP=0.4479). Clinical meaning: Minimum of NN intervals – shortest R-R interval', ’’,
'3. PPG_AUCso_nu_p25: ↓ Lower values (Low importance, SHAP=0.3597). Clinical meaning: AUC shoulder to offset (normalized) – shoulder to diastolic area', ’’,
'4. PPG_ppgInterbeat_eigval2: ↑ Higher values (Low importance, SHAP=0.2685). Clinical meaning: 2nd eigenvalue of inter-beat PPG matrix – secondary interbeat PPG mode', ’’,
'5. HRV_HRV_CMSEn: ↑ Higher values (Low importance, SHAP=0.2600). Clinical meaning: Composite Multiscale Entropy – refined multiscale complexity measure', ’’,
'6. PPG_dpat_ms_entropy: ↑ Higher values (Low importance, SHAP=0.2507). Clinical meaning: Derivative of PAT over time – change in pulse arrival', ’’,
'7. HRV_HRV_ShanEn: ↑ Higher values (Low importance, SHAP=0.1937). Clinical meaning: Area of Poincaré ellipse – overall HRV scatter area', ’’,
'8. HRV_HRV_LFHF: ↓ Lower values (Low importance, SHAP=0.1379). Clinical meaning: Power in low frequency band (0.04–0.15 Hz) – sympathetic and parasympathetic activity', ’’,
'9. HRV_HRV_TINN: ↑ Higher values (Low importance, SHAP=0.1233). Clinical meaning: Triangular interpolation of NN histogram – HRV distribution width', ’’,
'10. HRV_HRV_MFDFA_alpha1_Asymmetry: ↑ Higher values (Low importance, SHAP=0.1169). Clinical meaning: Asymmetry of multifractal alpha1 – skewness of spectrum (short-term)', '']

Supplemental Table E7. Phenotype characterization provided by the LLM-based PIA agent on phenotype name, interpretation, and clinical characteristics using OpenAI's GPT-4o base model.

Phenotype SP-1:

1. PHENOTYPE NAME: "Reduced Autonomic Variability with Cardiac Irregularity"

2. PATHOPHYSIOLOGICAL INTERPRETATION:

- **Sepsis Mechanisms:**
    - The pattern of lower HRV metrics (e.g., HRV_HRV_SDNN, HRV_HRV_TP, HRV_HRV_CVI) suggests significant autonomic dysfunction, likely due to sepsis-induced stress and inflammation affecting the autonomic nervous system. This is indicative of impaired autonomic regulation and a reduced ability to adapt to physiological stressors.
    - The higher entropy in RR intervals (ECG_T_rr_ms_entropy) alongside lower skewness (ECG_T_rr_ms_skewness) suggests irregular heart rhythms, potentially due to sepsis-induced myocardial dysfunction or arrhythmias.
    - The increased chaos index (HRV_HRV_CD) further supports the presence of cardiac electrical instability.
- **Affected Organ Systems:**
    - **Cardiovascular System:** The combination of reduced HRV and irregular heart rhythms points to significant cardiovascular compromise, likely involving both autonomic dysregulation and direct myocardial effects.
    - **Autonomic Nervous System:** The reduced HRV metrics indicate a blunted autonomic response, with potential dominance of sympathetic over parasympathetic activity.
- **Autonomic Function Pattern:**
    - The specific HRV metrics suggest a state of autonomic imbalance, characterized by reduced parasympathetic (vagal) activity and potentially increased sympathetic tone, reflecting a stress response to sepsis.

3. CLINICAL CHARACTERISTICS:

- **Clinical Presentation:** Patients in this phenotype may present with signs of autonomic instability, such as tachycardia, irregular heartbeats, and possibly arrhythmias. They may exhibit symptoms of cardiovascular compromise, including hypotension or signs of distributive shock.
- **Hemodynamic Profile:** Likely to show signs of hemodynamic instability, with potential for low blood pressure and poor perfusion due to reduced vascular tone and cardiac output.
- **Respiratory Patterns:** Patients may exhibit compensatory tachypnea as a response to metabolic acidosis or hypoperfusion, although specific respiratory features are not highlighted in this cluster.

Phenotype SP-2:

1. PHENOTYPE NAME: "Reduced Complexity with Altered Cardiac Rhythm"

2. PATHOPHYSIOLOGICAL INTERPRETATION:

- **Sepsis Mechanisms:**
    - The pattern of lower HRV metrics such as Fuzzy Entropy and Katz Fractal Dimension suggests significant autonomic dysfunction, likely due to impaired autonomic regulation and increased physiological stress. This is common in sepsis, where systemic inflammation and stress responses disrupt normal autonomic balance.
    - Higher skewness in RR intervals indicates irregular heart rhythms, which may reflect sepsis-induced cardiomyopathy or arrhythmias, contributing to cardiovascular instability.
    - Lower PPG features such as AC skewness and AUC onset to shoulder suggest compromised peripheral circulation and reduced vascular tone, indicative of hemodynamic instability and potential distributive shock.
- **Affected Organ Systems:**
    - **Cardiovascular System:** The combination of altered HRV and ECG features points to significant cardiovascular compromise, including potential arrhythmias and impaired contractility.
    - **Autonomic Nervous System:** The reduced complexity in HRV metrics indicates autonomic dysfunction, a hallmark of sepsis pathophysiology.
    - **Peripheral Circulation:** Lower PPG features suggest impaired perfusion and vascular tone, affecting microcirculatory function.
- **Autonomic Function Pattern:**
    - The specific HRV metrics indicate a state of autonomic imbalance with reduced complexity, suggesting a shift towards sympathetic dominance or reduced parasympathetic activity, common in sepsis-related stress responses.

3. CLINICAL CHARACTERISTICS:

- **Clinical Presentation:** Patients may present with signs of cardiovascular instability, such as arrhythmias or irregular heartbeats, and symptoms of poor peripheral perfusion, such as cool extremities or delayed capillary refill.
- **Hemodynamic Profile:** Expect signs of distributive shock, including hypotension and reduced vascular resistance, potentially requiring vasopressor support.
- **Respiratory Patterns:** While specific respiratory features are not highlighted, compensatory tachypnea may be present as a response to metabolic acidosis or hypoperfusion.

Phenotype SP-3:

1. PHENOTYPE NAME: "Reduced Complexity with Altered Pulse Dynamics"

2. PATHOPHYSIOLOGICAL INTERPRETATION:

- **Sepsis Mechanisms:**
    - The pattern of lower HRV complexity measures (HRV_HRV_CMSEn, HRV_HRV_CD, HRV_HRV_ShanEn) suggests significant autonomic dysfunction, likely due to impaired autonomic regulation and increased physiological stress. This is common in sepsis, where systemic inflammation and stress responses disrupt normal autonomic control.
    - Higher HRV_HRV_SDNN indicates a paradoxical increase in overall HRV, which might reflect compensatory autonomic responses or variability due to arrhythmias.
    - Altered PPG features (e.g., increased PPG_A_AC_skewness and decreased PPG_mean_slope_os_mean) suggest changes in peripheral circulation, possibly due to vasodilation and altered arterial stiffness, common in sepsis-induced hemodynamic instability.
- **Affected Organ Systems:**
    - **Cardiovascular System:** The combination of HRV and PPG changes indicates significant cardiovascular involvement, with potential impacts on heart rate variability and peripheral perfusion.
    - **Autonomic Nervous System:** The reduced complexity in HRV metrics points to autonomic dysregulation, a hallmark of sepsis pathophysiology.
- **Autonomic Function Pattern:**
    - The specific HRV pattern, with reduced complexity and increased SDNN, suggests a state of autonomic imbalance where compensatory mechanisms are active but potentially overwhelmed by systemic stress and inflammation.

3. CLINICAL CHARACTERISTICS:

- **Clinical Presentation:** Patients may present with signs of autonomic dysfunction, such as tachycardia, and potentially arrhythmias due to the altered HRV metrics. Peripheral signs might include altered pulse strength and variability, reflecting changes in vascular tone and perfusion.
- **Hemodynamic Profile:** Expect hemodynamic instability characterized by potential hypotension due to vasodilation and altered vascular resistance. The increased pulse amplitude skewness suggests variability in pulse strength, possibly indicating fluctuating perfusion pressures.
- **Respiratory Patterns:** Respiratory patterns may include compensatory tachypnea, as the body attempts to manage oxygen delivery and CO2 clearance in the face of systemic stress.

Phenotype SP-4:

1. PHENOTYPE NAME: "Enhanced Parasympathetic Complexity with Altered Perfusion"

2. PATHOPHYSIOLOGICAL INTERPRETATION:

- **Sepsis Mechanisms:**
    - The pattern of higher HRV metrics such as HRV_HRV_pNN50, HRV_HRV_CMSEn, and HRV_HRV_ShanEn suggests an enhanced parasympathetic tone and increased complexity in

heart rate variability. This may indicate a compensatory autonomic response to stress or early sepsis, where the body attempts to maintain homeostasis.

- Lower HRV_HRV_LFHF indicates a reduced sympathetic activity relative to parasympathetic activity, which could reflect an imbalance in autonomic regulation often seen in sepsis.

- The lower PPG_AUCso_nu_p25 and higher PPG_ppgInterbeat_eigval2 suggest altered peripheral perfusion and potential changes in arterial stiffness or vascular tone, possibly due to systemic inflammation and microcirculatory dysfunction.

- **Affected Organ Systems:**

  - **Autonomic Nervous System:** The HRV patterns indicate significant autonomic involvement, with a shift towards parasympathetic dominance.

  - **Cardiovascular System:** Altered PPG features suggest changes in peripheral circulation and potential hemodynamic instability.

  - **Microcirculation:** Impaired perfusion and vascular tone changes are suggested by PPG metrics.

- **Autonomic Function Pattern:**

  - The autonomic function pattern, characterized by higher parasympathetic activity and complexity, suggests a state of compensated autonomic perturbation. This may represent an early or stable phase of sepsis where the body is actively trying to counteract stressors.

3. CLINICAL CHARACTERISTICS:

- **Clinical Presentation:** Patients may present with signs of autonomic imbalance, such as mild tachycardia or bradycardia, and potentially normal or slightly altered blood pressure due to compensatory mechanisms. They might exhibit signs of altered perfusion, such as cool extremities or delayed capillary refill, despite normal vital signs.

- **Hemodynamic Profile:** Expect a profile of relative hemodynamic stability with potential subtle signs of reduced vascular tone or early distributive shock.

- **Respiratory Patterns:** Respiratory patterns may include mild tachypnea as a compensatory response, but without overt respiratory distress or failure at this stage.

Supplemental Section E3.

HRV Magnitude Versus Complexity as Distinct Physiological Constructs in Derived Sepsis Phenotypes

Our findings highlight a critical distinction between HRV magnitude and HRV complexity, demonstrating that these dimensions capture fundamentally different aspects of cardiovascular regulation. Traditional HRV metrics such as SDNN, RMSSD, pNN50, and total power quantify the amplitude of beat-to-beat variability but are insufficient to characterize the structure or adaptability of autonomic control. In our cohort, groups SP-2 and SP-3 exhibited moderate to very high HRV magnitude, yet both showed markedly reduced nonlinear complexity, as evidenced by low

correlation dimension and suppressed composite multiscale entropy. This pattern indicates large but predictable fluctuations driven by a limited number of regulatory mechanisms, reflecting autonomic entrainment rather than physiological resilience. In contrast, group SP-4 demonstrated not only elevated HRV magnitude but also preserved multiscale complexity, consistent with rich, high-dimensional interactions among vagal, baroreflex, and peripheral vascular control loops. Importantly, group SP-1 further illustrates that apparent increases in entropy or dimensionality may arise from nonstationarity or instability in the setting of profound autonomic suppression, underscoring the need to interpret complexity metrics alongside HRV magnitude and physiological context. Collectively, these results show that high HRV magnitude alone does not equate to cardiovascular health; rather, the concurrent presence of high variability and preserved nonlinear complexity defines a super-normal, resilient autonomic–hemodynamic phenotype, with important implications for risk stratification and mechanistic phenotyping in sepsis and critical illness.

Supplemental Section E4.

Physiological Scope of PPG-Derived Features:

Photoplethysmography captures peripheral arterial pulsatile dynamics reflecting macrocirculatory arteriolar behavior, including arterial wall stiffness, pulsatile perfusion strength (AC amplitude), beat-to-beat pulse variability, and pulse wave transit time [Allen 2007]. While these metrics provide insights into peripheral vascular tone and arteriolar dynamics, they do not directly assess capillary-level microcirculation, which would require sublingual video microscopy or handheld vital microscopy [Ince 2018]. Therefore, references to 'peripheral vascular' or 'arteriolar' dynamics in this study reflect PPG-measurable macrocirculatory parameters, whereas inferences about microcirculatory function represent mechanistic hypotheses requiring future validation with direct microcirculatory imaging.

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