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## SUPPLEMENTARY MATERIAL

### Identification of sepsis subphenotypes: current methods and clinical implications in critical care practice. A structured narrative review

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**Supplementary Table 1. Summary of screening and selection process.**

| Items                       | Details  |
|-----------------------------|--|
| Search period               | October 2025 – November 2025   |
| Database used               | PubMed   |
| Search keywords             | Sepsis, Sepsis subphenotypes, Identification methods, sepsis phenotypes  |
| Publication years screened  | 2015 -2025   |
| Total records identified    | 136  |
| Records screened            | 83   |
| Full-text articles assessed | 30   |
| Studies included            | 26   |
| Screening process           | Title and abstract screening followed by full-text review  |
| Inclusion criteria          | English-language studies, full-text availability and articles describing methods for identifying sepsis subphenotypes.                             |
| Exclusion criteria          | Conference abstracts, editorials, duplicate records and studies without adequate methodological details  |
| Data extracted              | Study design, methods of subphenotypes identification, number of subphenotypes and clinical outcomes   |
| Study selection             | Articles were screened independently, and eligible studies were chosen based on relevance to subphenotype identification and clinical significance |

**Supplementary Table 2. Summary of subphenotype identification methods and subgroups identified.**

| Category                       | Technique used   | Number of subgroups identified | Reference |
|--------------------------------|--|--------------------------------|-----------|
| Clinical variable-based method | Time-aware soft-clustering                               | 6                              | [10]      |
|                                | Unsupervised clustering                                  | 4                              | [11]      |
|                                | Deep learning methods                                    | 3                              | [12]      |
|                                | Clustering   | 4                              | [13]      |
|                                | Latent profile analysis                                  | 4                              | [14]      |
| Biomarker-based method         | An unsupervised clustering analysis                      | 3                              | [15]      |
| Machine learning-based method  | Machine learning-based clustering approach               | 2                              | [16]      |
| Trajectory-based method        | 72-hour SOFA score trajectories, Dynamic time warping    | 4                              | [17]      |
|                                | Leukocyte trajectory patterns, Latent Class Mixed Model  | 8                              | [18]      |
|                                | A validated algorithm based on body-temperature patterns | 4                              | [19]      |
| Genomic/transcriptomic method  | RNA sequencing   | 4                              | [20]      |
|                                | Whole-blood leukocyte transcriptomic profiling           | 2                              | [21]      |

SOFA, sequential organ failure assessment.

**Supplementary Table 3. Comparative analysis of sepsis subphenotyping approaches.**

| Approach                       | Key features   | Strengths   | Limitations  |
|--------------------------------|--|---|--|
| Clinical variable-based method | Uses routine clinical parameters (vitals, labs, SOFA components) | Simple, widely available, easy to implement                     | Limited biological specificity, may oversimplify heterogeneity                             |
| Biomarker-based method         | Based on routine biomarkers values                               | Reflects underlying pathophysiology, better risk stratification | Variability in cutoffs, influenced by comorbidities, limited availability in some settings |
| Machine learning-based method  | Uses algorithms to analyze high-dimensional data                 | Identifies complex patterns, handles large datasets             | Limited interpretability, requires computational expertise, not real-time friendly         |
| Trajectory-based method        | Uses temporal trends (e.g., SOFA over 24–72 hrs)                 | Captures dynamic disease progression, prognostic value          | Requires repeated measurements, delayed classification                                     |
| Genomic/transcriptomic method  | Gene expression-based endotyping                                 | High biological precision, identifies molecular endotypes       | Expensive, time-consuming, not widely available  |

SOFA, sequential organ failure assessment.