Monaldi Archives for Chest Disease

eISSN 2532-5264 https://www.monaldi-archives.org/

Monaldi Arch Chest Dis 2026 [Online ahead of print]

To cite this Article:
Chinta D, Jeyasekaran V, Nagilla R, et al. **Identification of sepsis subphenotypes: current methods and clinical implications in critical care practice. A structured narrative review**. *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2026.3866

Submitted: 23-12-2025
Accepted: 22-04-2026

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

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Contributions: Divya Chinta: conceptualization, methodology development, manuscript drafting, and final preparation of the article. Vigneswaran Jeyasekaran, Ravi Nagilla: supervision and critical academic guidance throughout manuscript development. Sai Jaswanth Dasaganipalli: manuscript editing using appropriate software tools and assisted in final draft preparation. All authors read and approved the final manuscript.

Conflict of interest: the authors declare that they have no competing interests.

Ethics approval and consent to participate: not applicable.

Informed consent: not applicable.

Patient consent for publication: not applicable.

Availability of data and materials: not applicable. All information analyzed in this review was obtained from previously published studies.

Abstract

Sepsis demonstrates high variability in clinical manifestations, and patients with similar manifestations at the moment of diagnosis usually develop in very different ways. Such differences are explained by the difference in the immune response and organ reactions to infection. To counter this diversity, scientists have started to classify the patients into subphenotypes to determine whether the treatment can be planned in an individualized way. The objective of this review is to determine the methods of determining sepsis subphenotypes and their role in clinical practice. To conduct this review, a search in PubMed was conducted on studies published between 2015 and 2025. Papers that provided explicit information about the process of subphenotype identification were included. Articles that lacked the complete text, publications that were not published in English, and those that lacked the necessary methodological information were filtered out. In the chosen studies, there were several methods used, based on routinely available clinical variables; others were based on biomarkers, machine-learning techniques, time-varying trends in the dysfunction of organs, and transcriptomic data. Even though the methods are different, they have found many groups of patients who have significant differences in terms of inflammation, organ failure patterns, and response to treatment. According to the available evidence, there is no one such condition that sepsis represents, but rather a series of biologically different conditions. Subphenotyping can improve initial diagnosis and treatment, but most current methods are complex for clinical use. More efforts should be made to establish less complex tools, which may be implemented consistently at the bedside.

Key words: sepsis, sepsis subphenotype, organ dysfunction, individualized therapy.

Introduction

Sepsis continues to be a major worldwide health problem, with an estimated 48.9 million cases and 11 million deaths due to sepsis globally in 2017, representing about 20% of all global deaths, with the greatest impact in South Asia, sub-Saharan Africa and Southeast Asia [1]. However, the prevalence of sepsis is unknown in many low and middle income countries and the limits of the available data illustrate the difficulties in assessing the true worldwide burden of sepsis [2]. Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. In severe cases, this response can result in multi-organ dysfunction involving the lungs, cardiovascular system, kidneys and liver reflecting widespread immune and inflammatory dysregulation [3]. It impacts millions of the world's population annually, and it is a leading cause of death, despite the considerable achievements in the initial identification and early intervention [4]. The Sequential Organ Failure Assessment (SOFA) score is traditionally used to evaluate the functioning of organs, and a score of two or more points is deemed to be correlated with a significant increase in the risk of death. The evidence-based use of the quick Sequential Organ Failure Assessment (qSOFA) score in prehospital and emergency environments is a quick bedside assessment, and scores above two should suggest a greater risk of poor patient outcomes in suspected-infected patients [5].

Sepsis, although it has a homogeneous definition, is not a homogeneous clinical manifestation. Rather, it covers a wide range of host reactions, clinical patterns, and courses of illness. This heterogeneity has spawned much interest in defining subgroups, so-called sepsis subphenotypes, which can have common biological or clinical features. Identification of these subphenotypes can be used to better risk-stratify and enable more therapeutic choices that are more in line with the patient profile, an approach that is slowly becoming a potential avenue towards better outcomes in sepsis care [6]. Early recognition and timely management of sepsis, particularly in emergency settings, are critical for improving patient outcomes, further emphasizing the need for improved risk stratification and individualized therapeutic approaches [7].

Materials and Methods

This review was conducted as a structured narrative review to provide a comprehensive overview of methods used to identify sepsis subphenotypes. The PubMed database was searched in a structured literature search that aimed to identify the studies that outlined the methods of classifying sepsis subphenotypes. The search strategy entailed a combination of words such as "sepsis," "sepsis subphenotypes," "sepsis phenotypes," and "identification methods." Inclusion criteria were full-text, English language articles published in the last ten years (2015-2025) that described methods to identify sepsis subphenotypes. Titles and abstracts were initially screened for relevance, with priority given to those that provided a clear description of the methods used to identify subphenotypes. Studies with sufficient methodological detail and with appropriate study design were considered for inclusion. Then full-text articles were retrieved and evaluated in detail. Studies were excluded if they were conference abstracts, editorials, duplicate publications or lacked sufficient methodological detail. Data extracted from the included studies included study design, methods used for subphenotype identification, number of identified subgroups, and reported clinical outcomes. The screening and selection process was performed according to relevance to subphenotype identification and clinical relevance. The screening and selection process is summarized in *Supplementary Table 1.*

Key findings

Definition of sepsis and sepsis subphenotypes

According to the Third International Consensus (Sepsis-3, 2016), sepsis is a life-threatening condition due to which the dysfunction of the organs occurs as a consequence of an unsynchronized host response to infection. This new definition standardized clinical interpretation of sepsis, and it gave organ dysfunction as the main diagnostic factor [5]. Although there has been a common definition, so far, there is no global framework for sepsis that has been unanimously accepted as being used in categorizing the various subgroups and even subphenotypes [8]. The lack of standardized terminology is an indication of the high levels of biological and clinical variability identified among the patients. A phenotype is a collection of clinical, biological, or physiological traits observable in a group of patients. A subphenotype is a more narrow division of this broad phenotype, which varies in clinical manifestations, immune responses, or outcomes [9].

Clinical variable-based method

Investigators have used routinely collected clinical data to classify sepsis subphenotypes. A time-aware soft clustering algorithm for early Intensive Care Unit (ICU) data from the Medical Information Mart for Intensive Care IV (MIMIC-IV) and electronic Intensive Care Unit (eICU) databases. This approach captures temporal trends of clinical variables, so that patients can be clustered based on dynamic changes in organ dysfunction and not static measurements. The algorithm assigns patients to subphenotypes probabilistically, capturing overlapping clinical features. Six hybrid sub-phenotypes with organ dysfunction patterns using this approach.The most severe one was Hybrid Subphenotype 1, which had the worst clinical presentation and mortality rates and was followed by Subphenotypes 4, 5, and 6, which had milder clinical presentations and low mortality. The paper noted that the use of Temporal clinical trends enhance heterogeneity in sepsis development and its outcome [10]. Unsupervised clustering has been applied to 29 routinely measured clinical variables (including demographics, vital signs, inflammatory markers, and early organ-dysfunction phenotypes) to come up with four reproducible sepsis phenotypes (α, β, γ, δ). The clustering approach grouped patients based on similarities in their initial clinical profiles without predefined categories. The identified phenotypes were further validated across multiple datasets and using alternative clustering methods to ensure reproducibility. Additionally, these phenotypes were correlated with distinct biomarker patterns and clinical outcomes, highlighting their biological and clinical relevance. The α phenotype was the most frequent and mild clinical phenotype with reduced vasopressor needs. The β phenotype had a high number of chronic comorbidities, particularly renal disease. The γ phenotype was characterized by increased inflammatory response and pulmonary dysfunction, which was the most intense, whereas the δ phenotype was the most severe, with liver dysfunction, septic shock, and a death rate of up to 40%. These phenotypes exhibited different biological markers and pointed to the possibility of different responses to treatment [11]. Deep learning–methods have been applied to detect subphenotypes in sepsis associated acute kidney injury using data from MIMIC-III.A high dimensional feature set was built using laboratory values, vital signs and comorbidities measured from admission until 48 hours after diagnosis of AKI and a deep learning autoencoder was applied for dimensionality reduction and extraction of important latent features, which were clustered using an unsupervised K-means approach and found three different subphenotypes. Subphenotype 1 portrayed the least serious group, where Simplified Acute Physiology Score II (SAPS II) scores are lower, and comorbidities are lower, including liver disease. Subphenotype 2 proved to have the highest incidence of chronic kidney disease, whereas Subphenotype 3 had the highest overall incidence of illness severity. There was an evident outcome gradient (the necessity to use dialysis increased to 4% in Subphenotype 1, to 7% in Subphenotype 2, and to 26% in Subphenotype 3, and 28-day mortality increased to 23%, 35%, and 49%). These results confirm significant biological and clinical heterogeneity of sepsis-related Acute kidney injury (AKI) and reveal the usefulness of data-driven methods in sorting out risk and treatment differences [12]. Clinical data–driven clustering approaches have identified subphenotypes in sepsis-associated liver dysfunction.Using data from the MIMIC-IV database, the authors applied unsupervised K-means clustering to clinical variables obtained within the early phase of ICU admission to derive four distinct subphenotypes (α, β, γ, δ). These subphenotypes were subsequently validated in an independent eICU cohort, demonstrating reproducibility. Subphenotype α was the gravest of them and was characterized by shock and dysfunction in multiple organs. Subphenotype β had significantly high levels of bilirubin and high levels of underlying liver disease with coagulopathy. Subphenotype γ was a group mainly composed of older patients and contained the largest percentage of chronic kidney disease. The most benign cluster was Subphenotype δ, which showed the lowest rates of 28-day and in-hospital mortality and was characterized by a high level of Gamma-Glutamyl transferase (GGT) despite the relatively lower bilirubin concentrations. These trends underscore different clinical manifestations in sepsis-associated liver dysfunction (SALD) and indicate that liver-related subphenotypes have different prognostic consequences [13]. A Retrospective study with latent profile analysis of standard clinical and laboratory data to identify subclasses of sepsis and to compare the purpose of different volumes of fluid resuscitation.Input variables were selected from multiple organ systems including hematological (platelet count, coagulation parameters), renal (creatinine, urine output), neurological (GCS), circulatory (blood pressure, vasopressor use) and respiratory parameters. Latent profile analysis is a model based clustering approach that identifies hidden sub-groups by clustering patients with similar patterns across these variables. The best number of profiles was decided on the basis of statistical fit indices such as Bayesian information criterion and bootstrap likelihood ratio testing and the model was tested in a different cohort. Four profiles were found: the most common and least dangerous (Profile 1); the one that is primarily characterized by respiratory dysfunction (Profile 2); the one that is the most severe with multiorgan dysfunction of the renal, coagulation, and hepatic systems accompanied by shock (Profile 3); and the one that is the most numerous with impaired neurology (Profile 4). The clinically meaningful heterogeneity was observed as mortality was significantly different among profiles, including Profile 3 (45.4%), Profile 4 (27.4%), Profile 2 (18.2%), and Profile 1 (16.9%) [14].

Biomarker-based method

Biomarker-based approaches have been used to identify immune-related subtypes in sepsis using routinely available immunological and inflammatory markers. In one such study involving 236 sepsis patients, immune-based subtypes were identified using a range of immunological variables. The variables included lymphocyte subsets (T cell, B cell, NK cell, and total white blood cell count), biomarker circulation of cytokines (IL-6, IL-8, and IL-10), and demographic and clinical factors. The authors applied K-means clustering to standardized immune and inflammatory markers to group patients based on similarities in their immune response profiles, and the optimal number of clusters was determined using the elbow method and silhouette analysis. and found three types of immune subtypes: a high immune activation group of patients with high lymphocytic counts and low levels of cytokines; an intermediate group of patients with moderate immune responses; and a hyperinflammatory-immunosuppressed type of patients with high levels of cytokines and low lymphocytic counts.

The high activation group, as well as the hyperinflammatory-immunosuppressed group, had a high level of mortality 28 days later. These results indicate that the comparison of routine immune markers can be useful in identifying clinically significant subgroups and might be useful in guiding risk stratification earlier and more personalised therapeutic interventions [15].

Machine learning-based methods

Machine learning–based approaches have been used to study a large cohort of 8,817 sepsis patients . Algorithms were applied to clinical datasets to detect hidden patterns and clinically meaningful subphenotypes that might not have been readily discernible using conventional analytical methods . In particular, an unsupervised K-means cluster algorithm was used to classify patients by similarity in multivariable clinical and laboratory parameters. Continuous variables were standardized to z-scores prior to clustering to be comparable across features. The optimal number of clusters was determined using standard evaluation metrics. Two different subphenotypes were determined. Subphenotype B was characterized by elevated lactate, glucose, creatinine, white blood cell count, and sodium; greater heart rate; and reduced body temperature, platelet count, systolic blood pressure, and hemoglobin with a higher PaO2/FiO2 ratio than Subphenotype A. Patients with subphenotype B had a higher rate of mortality, which is indicative of a more severe clinical picture [16].

The method's clinical utility is that it can be quickly implemented at the bedside since it is based on routinely gathered parameters. These models can adjust early risk stratification, inform triage and degrees of surveillance, and assist in disclosing the high-risk patients who might need closer attention and more vigorous supportive care.

Trajectory-based methods

Trajectory-based methods categorize patients with sepsis based on their variations in organ dysfunction across time as opposed to individual measurements. A study examined 72-hour SOFA score dynamics in four intensive care unit cohorts to identify sepsis subphenotypes based on patterns of organ dysfunction over time. Using dynamic time warping (DTW), a technique that measures similarity between time-series data, the authors compared the temporal progression of SOFA scores among patients. Hierarchical agglomerative clustering was then applied to group patients with similar trajectory patterns into distinct subphenotypes. Four SOFA trajectory-based sepsis subphenotypes were identified. These were Rapidly Worsening (characterized by SOFA scores >7 at 72 hours), Delayed Worsening (stabilization followed by worsening), Rapidly Improving (persistent improvement to SOFA <3), and Delayed Improving (worsening followed by improvement of the condition). The described trajectories showed significant variations in the patterns of organ dysfunction, even with the same standard care, implying different underlying biological reactions. Identification of these temporal patterns can be used to help in early risk stratification as well as to aid more focused management approaches [17]. Another study discovered sepsis subphenotypes according to the dynamic changes in leukocyte count during the initial 96 hours of admission to the ICU. Latent Class Mixed Models (LCMM) were applied to longitudinal leukocyte trajectories to classify patients into distinct subgroups based on temporal patterns. The optimal number of subphenotypes was determined using model selection criteria, and findings were validated in an external cohort. Eight trajectory-based subphenotypes were obtained with a significant difference in 28-day mortality and organ-support needs. Patients with constantly high leukocyte patterns demonstrated hyperinflammatory patterns and the worst results, but those with constantly low leukocytes also demonstrated more mortality patterns, but with different organ support requirements, including invasive mechanical ventilation, vasopressor use, and renal replacement therapy. The XGBoost model based on baseline ICU variables also allowed predicting high-risk subgroups [18]. A study categorized 3,576 suspected-infected patients into four temperature-trajectory subphenotypes based on body temperature measurements recorded over the first 72 hours of hospitalization. A validated temperature trajectory algorithm was applied, in which each patient's temperature pattern was compared with predefined reference subphenotypes, and Patients were assigned to the subphenotype whose temperature pattern most closely matched their individual trajectory. Groups of hyperthermic fast resolvers (23%), hyperthermic slow resolvers (16%), normothermic patients (47%), and a subgroup of hypothermic patients (14%) were identified with significant differences in mortality. The hypothermic group recorded the highest mortality (14.2%), whereas hyperthermic slow resolvers (6%), normothermic patients (5.5%), and hyperthermic fast resolvers (3.6%) died less. Among 31 evaluated inflammatory, immune, and coagulation biomarkers, 20 were significantly different in subphenotypes; hyperthermic groups displayed high levels of cytokines, and hypothermic patients displayed low levels of cytokines accompanied by increased levels of coagulation-related biomarkers such as Angiopoietin-1, thrombomodulin, and tissue factor, suggesting a coagulopathy-dominant profile [19].

Genomic/transcriptomic methods

Subphenotypes of sepsis have been identified in genomic and transcriptomic methods, which offer an understanding of the underlying immune and biologic pathways. These techniques are able to measure differences in molecules that cannot be detected using clinical or routine laboratory information. RNA sequencing of peripheral blood samples has been performed in 494 sepsis patients to profile the host immune response. Gene expression data were processed and normalized, and Topological Data Analysis (TDA) was applied to group patients based on similarities in their gene expression profiles. This approach enables identification of biologically distinct subphenotypes while capturing the continuous nature of immune responses, allowing some overlap between groups. Four molecular subtypes were obtained, which had different biological profiles, and the risk of death at 28 days varied. Its low-mortality immunocompromised subtype had an intact expression of adaptive immune genes, and three criteria of high-mortality subtypes were immunosuppression, hyperactivity of innate immunity, or distortion of immunometabolic pathways, such as the inhibition of heme biosynthesis [20]. A study Compared the whole-blood leukocyte transcriptomes of 265 patients who were reported to have sepsis caused by community-acquired pneumonia. Genome-wide gene expression profiling was performed, and patients were grouped based on similarities in their transcriptional patterns. Two sepsis response signatures (SRS1 and SRS2) were identified and validated in an independent cohort. sepsis response signature 1(SRS1) was an immunosuppressed type characterized by T-cell exhaustion and lower expression of human leukocyte antigen (HLA) class II and was characterized by much greater 14-day deaths than SRS2, which exhibited a more maintained immune response [21]. *Supplementary Table 2* provides an overview of the methodologies used to identify sepsis subphenotypes, along with the number of subgroups identified by each method

Clinical significance

It has been demonstrated through previous studies that the heterogeneous nature of sepsis makes it significant to find out different subgroups, as these findings can be useful in the earlier stratification of risks, individualized treatment, and understanding of prognosis. Recent evidence, Recent evidence has shown that outcome prediction can be greatly enhanced with the help of phenotype-based modeling, which provides evidence of the utility of clinical subphenotyping in accurate sepsis care [22]. Using clustered clinical data have identified four groups of sepsis and found that each of them had diverse mortality risks and diverse responses to the use of vasoactive drugs. These results imply that treatment choices, particularly of vasoactive drugs, can be required to be modified by phenotype to optimize patient outcomes [23].

Discussion

The sepsis subphenotype identification has demonstrated a high level of potential to enhance risk assessment and assist in a risk-focused approach to patient therapy in critically ill patients. Yet, heterogeneity that is inherent to sepsis still affects clinical manifestation, response to treatment, and outcomes despite the increased research and restricted numbers of specialized treatment methods [24]. Different methods have been used to identify subphenotypes in different studies and comparison of methods suggests important trade-offs. Similar results have been reported by several studies. For instance, clinical phenotype-based classifications have shown that routinely available clinical data can be used to identify distinct subgroups of patients with different outcomes, which can be used at the bedside [11]. In contrast, transcriptomic and biomarker-based studies have identified biologically distinct endotypes associated with differences in immune response and mortality [15,21]. These observations are consistent with this review, where clinically feasible models provide feasibility and biologically driven models provide deeper mechanistic insight, but are less feasible for real time clinical use. All these shortcomings highlight the importance of multimodal approaches that would combine regularly available clinical data with important biological factors to improve predictive accuracy without undermining clinical feasibility. The translation of these findings into the frontline practice can potentially contribute to the reduction of unneeded interventions in the low-risk groups and timely escalation of care in high-risk hyper- or hypoinflammatory subphenotypes. Although the results are encouraging, several obstacles, such as a lack of standardized classification systems and inconsistent methodology across studies and a lack of external validation on different patient populations, persist. Subsequent research efforts should be aimed at coming up with straightforward, reproducible, and treatment-responsive phenotyping instruments that can be easily integrated into automatic electronic health-record systems to hasten the implementation of subphenotype-directed decision-making in daily sepsis care. In addition to these methodological considerations, further conceptual clarity is required in understanding sepsis heterogeneity. An important distinction in sepsis research is that between phenotypes and endotypes. Phenotypes are clinically observable characteristics and data that are readily available, while endotypes are different biological mechanisms underlying the disease process [25]. This distinction is clinically relevant as patients with similar phenotypic presentations may have very different immune responses and treatment courses.

Identifying hyperinflammatory and hypoinflammatory endotypes provides a biological rationale for the heterogeneity seen in sepsis and assists in explaining variability in therapeutic response. These differences have important implications for therapeutic targeting, as interventions that are beneficial in one subgroup may be ineffective or even harmful in another. This understanding is in line with the developing idea of precision medicine in sepsis, in which the combination of clinical features with readily available biomarkers may allow early identification of biologically distinct subgroups, and eventually more personalized treatment approaches. However, before widespread implementation in routine emergency and critical care practice, further validation, standardization and development of rapid, clinically feasible tools are needed.

Comparative synthesis of sepsis subphenotyping approaches

Different approaches to sepsis subphenotyping have different strengths, but also important limitations that impact on their clinical utility. Clustering methods based on clinical variables are relatively straightforward to use, with commonly available data, but may be lacking in biological specificity [10-14]. Biomarker-based approaches provide better pathophysiological insights but suffer from variability in cutoff values and availability in settings [15]. Machine learning techniques can be used to integrate high-dimensional data and identify complex patterns, and they have demonstrated potential in optimizing treatment strategies in sepsis; however, their interpretability and feasibility in real-time emergency settings are challenging [16,26]. Trajectory-based models capture the dynamic progression of organ dysfunction and may better reflect disease evolution but require repeated measurements and may not be practical in resource-limited environments [17-19].

Transcriptomic profiling accurately classifies molecular subtypes and has uncovered distinct endotypes, such as hyperinflammatory and hypoinflammatory conditions. However, the bedside utility is hindered by high costs, technical complexity and slow turnaround times [20,21].

In the end, there is no one best approach, universally. A holistic approach of clinical variables, biomarkers, as well as dynamic trends may provide a more feasible and clinically relevant framework for sepsis subphenotyping, especially in the emergency and critical care settings. The strengths and limitations of the various approaches to sepsis subphenotyping are summarized in *Supplementary Table 3.*

Strengths and limitations of this review

Strengths

‣ This review presents a comprehensive view of the current state of the art in sepsis subphenotyping, combining evidence from clinical variable-based approaches, biomarker-driven studies, machine learning techniques, trajectory-based analyses and transcriptomic profiling.

‣ It highlights the heterogeneity of sepsis and stresses the clinical importance of subphenotype identification for better risk stratification and understanding of disease mechanisms.

Limitations

‣ The review was performed as a structured narrative review and not according to formal systematic review methodology, therefore study selection may be subject to selection bias.

- ‣ Included studies are heterogeneous in terms of datasets, variables and analytical approaches, which limits the direct comparability of findings.
- ‣ Most included studies are retrospective and from high-resource settings which may limit applicability to broader populations.
- ‣ Many sepsis subphenotyping approaches are not yet validated for bedside implementation in real-time and thus limit their clinical applicability.
- ‣ A major challenge remains the lack of standardized definitions and classification frameworks of sepsis subphenotypes.

Conclusions

Existing literature shows that sepsis is not a single unit but a kind of spectrum of various clinical and biological conditions. The identification of these subphenotypes helps us to improve our perception of variability in the patient population and explain why people with similar symptoms or different responses to the same therapy differ. The employed studies in this paper suggest that there are several approaches that have been applied to find the sepsis subphenotypes, such as those that rely on clinical data, machine-learning models, pattern trajectories, and genomic or transcriptomic analyses. The critical outcomes between these subgroups are also significantly different in terms of responses to treatment and risks of mortality.

Although a large part of these methods is useful in terms of research, certain methods are too complex or resource-dependent to be applied in practice. Further attempts should be undertaken to develop more simplified and standardized procedures that could be easily implemented in routine clinical practice and that could improve the outcomes of sepsis patients.

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Online supplementary material

Supplementary Table 1. Summary of screening and selection process.

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

Supplementary Table 3. Comparative analysis of sepsis subphenotyping approaches.