Clinical phenotypes of sepsis: a narrative review

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Contributions: (I) Conception and design: Q Zhou; (II) Administrative support: Q Zhou; (III) Provision of study materials or patients: Q Zhou; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

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Background and Objective: Sepsis, characterized by an aberrant immune response to infection leading to acute organ dysfunction, impacts millions of individuals each year and carries a substantial risk of mortality, even with prompt care. Despite notable medical advancements, managing sepsis remains a formidable challenge for clinicians and researchers, with treatment options limited to antibiotics, fluid therapy, and organ-supportive measures. Given the heterogeneous nature of sepsis, the identification of distinct clinical phenotypes holds the promise of more precise therapy and enhanced patient care. In this review, we explore various phenotyping schemes applied to sepsis.

Methods: We searched PubMed with the terms "Clinical phenotypes AND sepsis" for any type of article published in English up to September 2023. Only reports in English were included, editorials or articles lacking full text were excluded. A review of clinical phenotypes of sepsis is provided.

Key Content and Findings: While discerning clinical phenotypes may seem daunting, the application of artificial intelligence and machine learning techniques provides a viable approach to quantifying similarities among individuals within a sepsis population. These methods enable the differentiation of individuals into distinct phenotypes based on not only factors such as infectious diseases, infection sites, pathogens, body temperature changes and hemodynamics, but also conventional clinical data and molecular omics.

Conclusions: The classification of sepsis holds immense significance in improving clinical cure rates, reducing mortality, and alleviating the economic burden associated with this condition.

Keywords: Sepsis; heterogeneity; phenotype

Introduction

Sepsis, characterized as a dysregulated immune response to infection resulting in acute organ dysfunction, impacts millions of individuals annually and presents a significant risk of death, even with prompt care (1). It accounts for over half of in-hospital deaths and stands as the costliest disease in healthcare, constituting $20.3 billion or 5.2% of all hospitalization expenses (2). A recent study estimated that in 2017, sepsis affected 48.9 million people globally and caused 11 million deaths worldwide (3). As a result, the World Health Organization has made sepsis a global health priority (4).

Despite significant medical advances, sepsis remains a huge challenge for clinicians and trialists, with treatment options limited to antibiotics, fluid therapy, and organ support measures (5). Sepsis affects a heterogeneous population in terms of the site of infection, organism type, genetic background, and coexisting host conditions. Hence, personalized patient care is recommended to

Table 1 The search strategy summary

Items	Specification
Date of search	09/08/2023–11/08/2023
Databases and other sources searched	PubMed
Search terms used	(Clinical phenotypes) AND (sepsis)
Timeframe	2000–2023
Inclusion and exclusion criteria	Inclusion criteria: any study type; English formatted studies
	Exclusion criteria: editorials or articles lacking full text were excluded
Selection process	The selection process was conducted independently by both authors, with no consensus obtained externally

enhance survival rates (6). Ideally, a precision medicine approach would leverage a predictive enrichment tool, such as a clinical risk factor, plasma biomarker, or gene expression pattern, to identify patients most likely to benefit from the therapy in question (7). We present this article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-114/rc).

Methods

We searched PubMed with the terms "Clinical phenotypes AND sepsis" for any type of article published in English up to September 2023 (*Table 1*). Retrieved articles were screened based on their title and abstracts. Articles of potential interest were further selected by giving the preference to well-designed studies, large patient populations, and systematic reviews or meta-analyses of the literature. Additional literature was retrieved from the reference list of articles identified in the PubMed search.

Key content and findings

Definitions of sepsis subtypes

Currently, there exists no international consensus regarding the terminology employed for sepsis classification. Reddy *et al.* (8) proposed that a phenotype is defined by a set of features shared among patients who exhibit a common syndrome or condition. In contrast, a subphenotype describes a set of features that distinguishes subgroups within that phenotype, characterized by a distinct biological mechanism of disease. This mechanism is often associated with an anticipated response to treatment shared by a subgroup of patients, as indicated by common mortality risk, clinical course, or treatment responsiveness.

In recent years, the surge in genomics, transcriptomics, proteomics, and metabolomics, coupled with advancements in data analysis tools, has witnessed exponential growth in identifying novel disease subgroups (subphenotypes). This growth has resulted in numerous clinical and biological insights into sepsis (9-14). Machine learning offers distinct advantages in the analysis of vast amounts of complex high-dimensional data and is currently extensively applied in the in-depth analysis and mining of medical data. It stands as a crucial and widely utilized method for investigating sepsis classification and has gained widespread application (15).

Typing of sepsis subtypes

Sepsis classification based on infectious diseases

Sepsis can be categorized into two subtypes based on the nature of the infectious disease: medical and surgical. A nationwide survey conducted in Spain (16) defined patients with sepsis who underwent surgery, excluding tracheotomy, as having surgical sepsis, relying on discharge information. The findings revealed that surgical sepsis constituted 26% of cases, with internal sepsis being more prevalent, comprising 74% of cases.

Scheer *et al.* (17) observed variations in the primary site of infection between patients with medical and surgical sepsis. Among those with medical sepsis, the lungs emerged as the most frequent primary site of infection (42.0–56.7%), while for patients with surgical sepsis, the abdominal cavity ranked as the predominant site (48.4–64.4%). Furthermore, individuals with internal sepsis were predominantly affected by community-acquired infections, whereas those with surgical sepsis were primarily affected by hospital-acquired

and intensive care unit (ICU)-acquired infections.

In a study by Zhou *et al.* (18) examining the clinical characteristics of patients with internal sepsis, it was found that the incidence of lung infections was higher among elderly patients compared to their younger counterparts (73.6%). Internal sepsis constitutes the majority of sepsis cases, with pulmonary infections being the most prevalent type.

Sepsis classification based on infection sites

Chou *et al.* (19) conducted a comprehensive analysis of hospitalization data encompassing 7,860,687 adult sepsis patients, categorizing infection sites as follows: urinary and reproductive system (36.70%), lower respiratory tract (36.55%), circulatory system (systemic fungal infections 9.22%, primary bacteremia 6.96%), skin (8.12%), abdomen (5.32%), catheter (5.10%), musculoskeletal system (2.95%), biliary tract (0.66%), and others (21.29%). The top three highest mortality rates were associated with abdominal infections (30.65%), lower respiratory tract infections (27.70%), and biliary tract infections (25.48%).

In a study by Chen *et al.* (20), spanning 11 years and covering 1,259,578 sepsis patients, lower respiratory tract infections emerged as the most prevalent causes of sepsis with the highest mortality rates. He *et al.* (21) included 483 sepsis patients, revealing that lung infections accounted for 56.3% of cases, abdominal infections for 37.3%, and infections at other sites for 6.4%. In comparison to patients with abdominal infections, those with pulmonary infections were older, exhibited higher Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores, experienced more fungal and viral infections, and had an elevated risk of developing acute kidney injury and requiring continuous renal replacement therapy. Multivariate analysis demonstrated that pulmonary infection was an independent risk factor for both mortality and poor quality of life one year after sepsis.

These studies collectively indicate that clinical outcomes in sepsis, induced by infections at different sites, vary significantly. The lungs stand out as the most common site of infection for sepsis, with patients suffering from sepsis caused by lung infections demonstrating the highest disease severity and mortality rates. Additionally, pulmonary infections are identified as independent risk factors for both mortality and poor quality of life one year after sepsis.

Sepsis classification based on the pathogen

Sepsis is a dysregulated immune response to infection

resulting in acute organ dysfunction involving various pathogens, with bacteria being the most prevalent. A national survey in Spain revealed that gram-positive bacterial infections account for 33.6–39.4% of cases, showing a declining trend. Gram-negative bacteria, on the other hand, constitute 56.3–64.5%, exhibiting an increasing trend. Anaerobic infections contribute to 1.4–1.8%, while fungi account for 6.1–9.4% (16). Bacteria represent about 70% of septic pathogens, while viruses constitute only 1%, but maybe this is a limitation of diagnostics and will also vary enormously by time and place. Notable viruses include dengue fever virus (27%), rhinovirus (23%), influenza virus (17%), and respiratory syncytial virus (12%) (22).

The global outbreak of coronavirus disease 2019 (COVID-19) in 2019 has brought viral sepsis to the forefront of research, with approximately 5% of COVID-19 patients developing sepsis or septic shock, significantly elevating the risk of death (23). Ren *et al.* (24) conducted a comparison of the clinical characteristics of 21 patients with viral sepsis caused by severe acute respiratory syndrome coronavirus 2 with those of 46 patients with bacterial sepsis. In contrast to patients with viral sepsis, those with bacterial sepsis exhibited more severe organ function damage and poorer clinical outcomes, possibly linked to different immune responses. A key feature of immune imbalance in viral sepsis is a reduction in T lymphocytes and their subpopulations, whereas bacterial sepsis is characterized by excessive immune activation, leading to sustained immune suppression and multiple organ dysfunction (24).

Sepsis classification based on body temperature change trajectory

Body temperature values provide non-invasive data easily accessible at the bedside, offering insights into the patient's potential immune status. Furthermore, abnormal body temperature may serve as prognostic information for infected patients. Bhavani *et al.* (9) employed group-based trajectory modeling of repeated temperature measurements to identify sepsis subphenotypes. Four subtypes were discerned: hyperthermic slow resolvers (mortality, 10.2%), hyperthermic fast resolvers (mortality, 3%), normothermic (mortality, 4.5%), and hypothermic (mortality, 9.0%). The hypothermic slow resolvers tended to be older, while the hyperthermic fast resolvers exhibited higher serum C-reactive protein concentrations and faster erythrocyte sedimentation rates. Subsequently, Bhavani *et al.* (25) delved deeper into the correlation between body temperature trajectory and persistent cytokine subtypes,

these subphenotypes could play a role in the bedside identification of cytokine profiles in patients with sepsis.

An increasing number of researchers are exploring different facets of the phenotypic relationship between temperature and mortality in sepsis patients. For instance, in a prospective cohort study encompassing 1,184 sepsis patients across 59 ICUs in Japan, Ito *et al.* investigated the association between hypothermia and mortality based on body mass index (BMI). Their findings suggested that patients with body temperature <36 ℃ (hypothermia) had a higher in-hospital mortality rate than that had by those without hypothermia in the normal BMI group (25/63, 39.7% *vs.* 107/549, 19.5%); however, this was not true for patients in the low or high BMI groups (26). Given the accessibility of body temperature trajectory data, it is anticipated to evolve into an auxiliary tool for identifying sepsis subtypes.

Sepsis classification based on hemodynamics
Hemodynamics constitute another crucial clinical trait that aids in phenotyping critically ill patients with sepsis. Septic shock is specifically defined as persistent hypotension necessitating vasopressors to maintain a mean arterial pressure of 65 mmHg, even after adequate volume resuscitation (5).

In a study by Zhu *et al.* (27), data from a substantial medical database comprising 3,034 septic patients admitted to an ICU were extracted. Through trajectory analysis, seven distinct systolic blood pressure (SBP) trajectories were identified. Class 1, representing 36.9% of samples, exhibited steady SBP values around 100 mmHg. Class 2, constituting 7.5% of cases, maintained a stable SBP trend with a mean value of approximately 82 mmHg. Class 3 (8.4% of cases) demonstrated a gradual increase in SBP from 140 mmHg with a stable trend. Class 4 (21.3% of cases) displayed a steadily increasing SBP, progressing from 110–120 mmHg to 120–130 mmHg. Class 5 (15.3% of cases) saw a rapid decrease in SBP from around 130 to 100 mmHg. Class 6 (8.2% of cases) experienced a rapid decrease in SBP from 150–160 to 110–120 mmHg. Class 7 (2.8% of cases) featured an initial increase in SBP followed by a decrease, with an average SBP exceeding 160 mmHg, higher than other classes. The in-hospital mortality rates for patients in trajectory classes 1–7 were 25.5%, 40.5%, 11.8%, 18.3%, 23.5%, 13.8%, and 10.5%, respectively. Notably, Class 2 exhibited the lowest SBP and the highest risk of mortality, while Class 3 had the lowest mortality risk. The SBP trajectory of Class 3 could serve as a blood

pressure management target for sepsis patients within 10 hours of admission, offering guidance for physicians. Cox proportional hazards regression analysis indicated that Class 6 had a better prognosis than Class 2, highlighting that a persistent hypotensive state is associated with a worse prognosis than a substantial decrease in SBP. This insight enables clinicians to identify high-risk patients early on, facilitating timely treatment interventions.

Recently, Geri *et al.* (28) delineated five distinct hemodynamic phenotypes in 360 patients with septic shock, utilizing clinical and echocardiographic parameters as the basis for classification: cluster 1, the well resuscitated (16.9%); cluster 2, left ventricular (LV) systolic dysfunction (17.7%); cluster 3, LV hyperkinesia (23.3%); cluster 4, right ventricular failure (22.5%); and cluster 5, sustained hypovolemia (19.4%). ICU mortality rates in clusters 1, 2, 3, 4, and 5 were 21.3%, 50.0%, 23.8%, 42%, and 38.6%, respectively. By recognizing and differentiating early septic patients among different hemodynamic phenotypes, individualized hemodynamic support, such as with vasopressors, could be implemented. Inotrope infusion and fluid resuscitation could be tailored to the specific needs of each phenotype.

Papin *et al.* (29) conducted a retrospective analysis of 6,046 patients with sepsis admitted to the ICU, examining the loci of infection. Their study revealed six distinct clusters: young patients without any comorbidities admitted to the ICU for community-acquired pneumonia (40%); young patients without any comorbidities admitted to the ICU for meningitis or encephalitis (4%); elderly patients with chronic obstructive pulmonary disease admitted to the ICU for bronchial infection with few organ failures (6%); elderly patients with several comorbidities and organ failures (27%); patients admitted after surgery with a nosocomial infection (15%); young patients with immunosuppressive conditions [e.g., acquired immunodeficiency syndrome (AIDS), chronic steroid therapy, or hematologic malignancy] (8%). These clusters exhibited significant differences in both early and late mortality groups (P<0.001), even after adjusting for the severity of organ dysfunction (SOFA score) and the year of ICU admission.

Sepsis classification based on conventional clinical data
Various investigators have endeavored to subclassify patients with sepsis using readily available clinical data. Zhang *et al.* (30) employed the Medical Information Mart for Intensive Care III (MIMIC III) database to identify four distinct sepsis sub-phenotypes based on clinical variables.

These sub-phenotypes were classified as follows: Profile 1 (baseline group, low mortality); Profile 2 (respiratory dysfunction); Profile 3 (multiple organ dysfunction, highest mortality); Profile 4 (neurological dysfunction). Notably, Profile 3 exhibited a favorable response to intravenous fluids in terms of mortality, while Profile 4 responded poorly to intravenous fluids.

In a retrospective analysis involving 63,858 patients across three observational cohorts (10), four novel sepsis phenotypes (α, β, γ, and δ) were derived, validated, and found to correlate with biomarkers and mortality. These phenotypes demonstrated diverse demographics, laboratory values, and patterns of organ dysfunction: The α subphenotype (prevalence, 33%; mortality, 2%) exhibited fewer abnormal laboratory values and less organ dysfunction than the others; The β subphenotype (prevalence, 27%; mortality, 5%) encompassed older patients with more chronic illnesses and greater renal dysfunction; The γ subphenotype (prevalence, 27%; mortality, 15%) featured more inflammation, lower albumin serum concentrations, and higher temperature than the others; The δ subphenotype (prevalence, 13%; mortality, 32%) displayed higher lactate levels, elevated aminotransferase levels, and more pronounced hypotension than the others. In this retrospective analysis, four clinical phenotypes were identified that correlated with host-response patterns and clinical outcomes, and simulations suggested these phenotypes may help in understanding heterogeneity of treatment effects. Further research is needed to determine the utility of these phenotypes in clinical care.

In the realm of sepsis classification based on multiorgan dysfunction, Knox *et al.* (31) conducted a pioneering study in 2015. Utilizing machine learning techniques, they clustered 2,533 septic patients from the emergency department to the ICU into four distinct phenotypes: (I) shock with elevated creatinine levels; (II) minimal multi-organ dysfunction syndrome; (III) shock with hypoxemia and altered mental status; and (IV) hepatic disease. Mortality rates in these clusters were 11%, 12%, 28%, and 21%, respectively. Regression modeling revealed differences in the association between clinical outcomes and predictors, including the APACHE II score.

Zador *et al.* (11) employed latent class analysis to discern distinct patient subgroups by considering demographics, admission type, and morbidity composition. The study delved into the prevalence of organ dysfunction, sepsis, and inpatient mortality within these subgroups, analyzing a comprehensive dataset of 36,390 patients sourced from the open-access MIMIC III dataset. The "cardiopulmonary" and "cardiac" subgroups, comprising 6.1% and 26.4% of the study cohort respectively, primarily included older patients with a notable prevalence of cardiopulmonary conditions. Meanwhile, the "young" subgroup, constituting 23.5% of the cohort, consisted of younger and healthier individuals. The "hepatic-addiction" subgroup, encompassing 9.8% of the cohort, comprised middle-aged patients with a mean age of 52.25 years [95% confidence interval (CI): 51.85–52.65]. This subgroup exhibited elevated rates of depression (20.1%), alcohol abuse (47.75%), drug abuse (18.2%), and liver failure (67%). Within the study cohort, the "complicated diabetics" and "uncomplicated diabetics" subgroups represented 9.4% and 24.8%, respectively. Notably, the hepatic-addiction subphenotype exhibited the highest mortality rates, followed by the cardiac, cardiopulmonary, and complicated diabetic subphenotypes. Zador *et al.*'s study identified distinct multimorbidity states that associate with relatively higher prevalence of organ dysfunction, sepsis, and co-occurring mortality. The findings promote the incorporation of multimorbidity in healthcare models and the shift away from the current single-disease paradigm in clinical practice, training, and trial design.

In retrospective studies utilizing clinical data for sepsis classification, researchers employed clustering analysis to assess demographic information, disease severity, clinical manifestations, and infection characteristics among septic patients. The utilization of clinical data for classification serves to enhance the applicability of research findings in clinical practice. However, the actual benefit of this classification for guiding treatment decisions remains to be definitively established and necessitates validation through large-scale multicenter prospective studies.

Sepsis classification based on molecular omics

Host genome mutations play an essential role in the heterogeneity of patients with sepsis and were identified to predict the susceptibility and prognosis of sepsis (32). For instance, two transcriptional sepsis-related response signals pathway were associated with immune function and prognosis of patients with sepsis (33). The initial subphenotype, SRS1, demonstrates gene expression patterns suggestive of immunosuppression, indicating phenomena such as endotoxin tolerance, T-cell exhaustion, and human leukocyte antigen (HLA) class II downregulation. Notably, patients with the SRS1 subphenotype exhibited higher mortality rates compared to those with the SRS2

subphenotype. Additionally, investigations have revealed a significant interaction between the SRS isoform and hydrocortisone treatment in patients with septic shock. Corticosteroid therapy, specifically, is associated with increased mortality in those with SRS2. Moreover, counterintuitive findings regarding the responsiveness to recombinant IL-1RA (34) and a retrospective analysis of the VANISH trial cohort (35) underscore increased mortality in SRS2 patients receiving corticosteroids (odds ratio, 7.9; 95% CI: 1.6–39.9), with no treatment effect observed for the SRS1 subphenotype. Research conducted by a Dutch group, utilizing machine learning and cluster analysis of whole blood genome-wide expression profiles, identified four sepsis subphenotypes termed Mars1–4 (13). Clinical data revealed differences in the incidence, SOFA score, and mortality of septic shock among patients with different phenotypes, while no significant difference was observed in concomitant diseases, APACHE IV score, or acute lung injury. Consistently, the Mars1 endotype was associated with the highest mortality, with a poor prognosis linked to a significant decrease in the expression of genes involved in innate and adaptive immune functions. In contrast, the low-risk Mars3 endotype exhibited increased expression of adaptive immune or T-cell functions. Mars2 and Mars4 endotypes were characterized by high expression of genes involved in pro-inflammatory (e.g., nuclear factor-κB signaling) and innate (e.g., interferon signaling) immune reactions. To enhance potential clinical application, a biomarker was derived for each endotype; BPGM and TAP2 reliably identified patients with the Mars1 endotype. Classifying heterogeneous sepsis populations into molecular endotypes may offer insights for targeted therapies for specific subgroups. The adoption of robust approaches to subdivision based on biomarker panels represents an imminent development in critical care, poised to significantly alter the research landscape.

The biological phenotypes of sepsis present a novel and intuitive means to distinguish heterogeneous patient populations. They enhance our understanding of human studies, provide prognostically informative insights, and carry potential treatment implications. Future studies should aim to deepen our knowledge of existing phenotypes while expanding the discovery of new ones. Crucially, the clinical utility of biological phenotypes urgently requires testing in prospective clinical trials.

Conclusions

The definition of sepsis has historically been broad, encompassing a wide range of patients at risk. This approach, while aiming for inclusivity, presents significant challenges due to the inherent heterogeneity in both clinical practice and research (36). Currently, many kinds of subtypes have been proposed, but their overlap and clinical implications remain unclear. This is partly due to the lack of comprehensive data within a single cohort to compute each subtype (37). The question arises as to whether each novel subtype strategy adds value for the patient or merely reinvents the wheel by duplicating existing subtypes. Clarifying this information is crucial for predictive enrichment in future trials (38). In recent times, genotyping and machine learning have emerged as the primary technologies driving sepsis research. A review of sepsis classification, diagnosis, treatment methods, and prognosis reveals a predominant focus on single data analysis in most studies. While some multidimensional studies have been well-segmented, there remains a substantial need for additional prospective studies. Despite the inherent difficulty in achieving sepsis classification, it holds immense importance in improving clinical cure rates, reducing mortality, and alleviating economic burdens. This stems from its potential to swiftly identify patients with sepsis, conduct comprehensive evaluations of their condition, predict prognosis, and establish effective classification and treatment strategies.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-114/rc

Peer Review File: Available at https://jtd.amegroups.com/

article/view/10.21037/jtd-24-114/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups. com/article/view/10.21037/jtd-24-114/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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