1.) **Review Title**

Do Subphenotypes Predict Treatment Responses in Sepsis? A Scoping Review

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7.) **Review Team Members and their Organizational Affiliations**

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8.) **Funding Sources**

None

9.) **Conflicts of Interest**

None

10.) **Collaborators**

None

11.) **Review Objective/ Research Question**

In adult patients with sepsis or septic shock, do subphenotypes predict individual treatment responses to given interventions?

We will define subphenotype as **at least one factor present at baseline** (before treatment is given) - whether a "risk factor, trait, diagnostic feature, expression marker [...] - that distinguishes the group from other groups of patients with the same phenotype" (based on Reddy et al., 2020) [1] with at least one factor being a **non-routine biomarker**. In this context, a “non-routine biomarker” means that the biomarker would not have been routinely assessed for patient care had the patient not been enrolled in the research study being reviewed (e.g., IL-6).

12.) **Searches**

The search strategies outlined below were developed in conjunction with an information specialist. Embase, Ovid MEDLINE, and Web of Science will be searched from inception to the date the search is conducted. In addition, a manual review of the bibliographies of eligible studies and relevant review articles will be performed.

The overall search will combine the following themes: Sepsis AND Predictive Enrichment AND (RCT OR Observational)

Keywords include:

Sepsis:

- Sepsis
- Septic shock
- ARDS

Predictive Enrichment:

- Biomarker
- Subclass
- Subtype
- Subgroup
- Endotype
- Subphenotype
- Phenotype
- Transcriptomics
- Proteomics
- Genomics
- Multi-omics
- Metagenomics
- Genetics
- Gene expression
- Metabolomics

- Latent class analysis
- Latent profile analysis
- Cluster analysis
- Heterogeneity
- Responder
- Non-responder
- Treatment failure
- Predictive enrichment
- Personalized medicine

RCT OR Observational:
- Randomized controlled trial
- Cohort studies
- Follow-up studies
- Longitudinal studies
- Prospective studies
- Retrospective studies
- Cross-sectional studies

13.) Background and Rationale

Septic shock is the leading cause of death in the intensive care unit with a mortality rate of approximately 20-40%[2-4]. It is caused by a severe infection and is associated with activation of inflammatory mediators initiated by the infectious pathogen[5-8]. The sequelae of septic shock are heterogenous and complex in nature, composed of a collection of signs and symptoms, which makes clinical diagnosis and treatment difficult. As such, there has been increased interest in subgrouping patients based upon various clinical, phenotypical, and biological characteristics to better understand the pathophysiology of the disease and to predict treatment responses in patients[1]. However, immense heterogeneity in the approaches used to classify sepsis subgroups, coupled with vague terminology and definitions in the field, have made the implementation of these findings challenging. The objective of this scoping review is to summarize available adult sepsis studies that use at least one baseline biomarker (e.g., cytokines, RNA, gene expression data), either alone or in combination with other factor(s), to subgroup patients into subphenotypes and assess their response to a given therapeutic intervention (either prospectively or retrospectively).

Ultimately, our goal is to better understand the utility of predictive enrichment in the treatment of adult sepsis. Predictive enrichment is a process within precision medicine which uses baseline biomarkers to categorize patients into subgroups that are predicted to have favourable responses to certain treatments, based on biological mechanism [9]. Furthermore, our findings could support the development of new consensus definitions, which re-frame sepsis as a collection of related yet distinct disease subsets (endotypes), rather than as a single heterogenous syndrome. We also intend to use the results of this project to support applications for future clinical trials.

As Reddy et al., 2020 proposed that true endotypes do not yet exist in sepsis [1], we will use the term subphenotypes instead. Reddy et al., 2020 define subphenotypes as: “A set of features in a group of patients who share a phenotype – such as shared risk factor, trait, diagnostic feature, expression marker, mortality risk, or outcome in response to treatment – that distinguishes the group from other groups of patients with the same phenotype (eg, hypoinflammatory vs hyperinflammatory ARDS, or sepsis response signature 1 vs sepsis response signature 2).” [1]. We will use a modified definition, as described above in section 11. However, note that other authors may use terms such as “endotype”, “subgroup” or “phenotype” interchangeably to refer to the same concept as “subphenotype”.

14.) **Participants / Population**

Inclusion: Adult human patients (age 18 years and older, or as defined in the study) with sepsis or septic shock (including ARDS, COVID) in all critical care settings (at least 50% admitted to ICU at inclusion)

Exclusion: Paediatric population (if a study includes both adult and paediatric datasets, only the adult data will be included)

15.) **Interventions**

Inclusion: Used at least one baseline, non-routine biomarker (e.g., cytokine, RNA) or omics data (e.g., gene expression, gene sets, proteomics, transcriptomics) to subgroup patients into subphenotypes and assess the treatment response to a given therapeutic intervention (either prospectively or retrospectively), either alone or in combination with other factor(s)

Exclusion: Prognostic analyses (i.e., only descriptive analyses on the differences in outcomes between groups)

Definitions:

Sepsis and septic shock studies: studies that include patients with sepsis, ARDS, COVID-19, as defined according to the individual paper

Subphenotype: see above modified Reddy et al., 2020 definition

16**.) Comparator(s)/Control**

Within a subphenotype, the comparator will be defined as the patients who did not receive the treatment (i.e., received placebo or standard of care)

17.) **Inclusion Criteria/Study Design**

Eligible articles include those involving adult patients in critical care settings (at least 50% admitted to ICU at inclusion) with sepsis or septic shock (including ARDS, COVID-19 etc.). Studies must use at least one non-routine biomarker obtained at baseline (e.g., cytokines, RNA, gene expression etc.) to identify sepsis subphenotypes and assess treatment responses to a given intervention (can be done either prospectively or retrospectively). Studies that compare identified sepsis subphenotype group(s) with a corresponding comparator group without the biomarker will also be included (e.g., observational with control arm, case-control etc.).

TITLE & ABSTRACT SCREENING	
Inclusion Criteria	**Exclusion Criteria**
1.Population: Adult human patients (18+ years old, or as defined by study authors) in any in-patient setting (ICU, ED, ward, etc.), diagnosed with sepsis or septic shock (including ARDS and COVID-19), stratified into at least 2 subphenotypes OR 1 subphenotype and 1 non-subphenotyped group 2. Subphenotyping must use at least 1 trait obtained at baseline (before treatment is	1. Population: In vitro studies, animal studies, children (<18 years old, or as defined by study authors) 2. Categorized patients into subgroups using only 1 trait 3. Categorized patients using a pre-established standardized score (e.g., MODS score) 4. Outcome: Solely prognostic (i.e., use subphenotypes to classify patients into groups with different likelihoods of survival, without

given), according to modified Leddy definition (though not all traits must be at baseline) 3.Intervention: Within each subphenotype, there must be at least 1 treatment (intervention) for sepsis or septic shock 4.Comparator: Within each subphenotype, there must be at least 1 comparator (i.e., placebo or standard of care) 5.Outcome: Assessed responses to treatment for sepsis or septic shock	looking at response to treatment) 5. Non-primary articles such as review articles 6. Dissertations, reports, conference abstracts
FULL-TEXT REVIEW Criteria that differ from article screening are underlined	
Inclusion Criteria	**Exclusion Criteria**
1.Population: Adult human patients (18+ years old, or as defined by study authors) in any critical care settings (at least 50% admitted to ICU at inclusion), diagnosed with sepsis or septic shock (including ARDS and COVID-19), stratified into at least 2 subphenotypes OR 1 subphenotype and 1 non-subphenotyped group 2. Subphenotyping must use at least 1 non-routine biomarker obtained at baseline (before treatment is given), according to modified Leddy definition (though not all traits must be at baseline) 3.Intervention: Within each subphenotype, there must be at least 1 treatment (intervention) for sepsis or septic shock 4.Comparator: Within each subphenotype, there must be at least 1 comparator (i.e., placebo or standard of care) 5.Outcome: Assessed responses to treatment for sepsis or septic shock 6.Language: English	1. Population: In vitro studies, animal studies, children (<18 years old, or as defined by study authors) 2. Categorized patients into subgroups using only 1 trait 3. Categorized patients using a pre-established standardized score (e.g., MODS score) 4. Outcome: Solely prognostic (i.e., use subphenotypes to classify patients into groups with different likelihoods of survival, without looking at response to treatment) 5. Non-primary articles such as review articles 6. Dissertations, reports, conference abstracts

18.) **Outcomes**

We will report on all outcomes in the included studies, including but not limited to mortality (at the furthest follow-up timepoint), clinical outcomes (e.g., organ support free days, organ dysfunction, length of stay in hospital etc.), biological outcomes (e.g., IL-6 levels). We will not report on safety outcomes.

19.) **Risk of Bias Analysis**

Two independent reviewers will conduct quality assessment on the methodology and heterogeneity of the approaches used in each included study. For randomized controlled trials, we will use Cochrane ROB. For non-randomized and observational studies, we will use Newcastle-Ottawa Scale and/or ROBINS-I. For assessing the quality of the methodologies used to determine sepsis subphenotypes, we will use PROBAST.

20.) **Study Selection and Data Extraction**

Two independent reviewers will review studies for inclusion and extract data into standardized, pre-piloted data collection forms/tables. Discrepancies will be resolved through discussion with a third-party team member.

21.) **Strategy for Data Synthesis**

Results will be described narratively and presented in tables and figures.

Table 1: Overall summary of included studies

- Author, Year
- Study name (if applicable)
- Country/ies
- Number of centres
- Study design (e.g., RCT, case-control, etc.)
- Eligibility criteria

Table 2.1: Study population and subphenotypes

Study population

- Sample size (n)
- Age (mean, range)
- Sex and gender (%)
- Race/ethnicity (%)
- Severity of illness score (e.g., APACHE-II, SOFA, MODS)

Subphenotypes

- Type of factors used in subphenotyping: clinical (clinical algorithm), biological (cytokines, RNA, health record labs), imaging, omics (cluster cytokines), demographic (gender, age)
- Describe methodology used to create subphenotypes (e.g., bioinformatics techniques, statistical analysis, machine learning)
- Description of subphenotype (e.g., corticotropin responder vs. non-responder)
  - Specify definition/cutoff for each
  - Provide sample size of each subphenotype
- Sample/data source of biomarker (e.g., tissue type (blood), sample type, timing of sample, methods of analysis)

Table 2.2: Interventions

- Description of intervention (e.g., medication name and dose)
- Timing of intervention
- Sample size of each subphenotype within each intervention arm

Table 2.3: Outcomes

- Describe primary and secondary outcomes, as applicable (e.g., mortality, organ support free days)
- Results (stats) for each subgroup

Table 3: Risk of bias table

- Depends on study design – see previous section

Table 4: Methodological table

- See previous section

22.) **Analysis of Subgroups**

There are no planned subgroup analyses.

23.) **Current Stage of Review**

A search for eligible studies was conducted on July 12, 2024 for this review.

24.) **Knowledge Dissemination**

Results will be disseminated through the Canadian Critical Care Translational Biology Group and shared with relevant stakeholders (e.g. Sepsis Canada) and presented at relevant local, national, and international conferences.

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