INPLASY PROTOCOL

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Monocytic HLA-DR expression and clinical outcomes in adult ICU patients with sepsis – a systematic review and meta-analysis

Waskowski, J[1]; Moolan-Vadackumchery, R[1]; Schefold, JC[1].

Review question / Objective: **The scope of this review was defined using PICOTS framework where 1) population: adult critically ill patients with sepsis or septic shock; 2) index prognostic factor: cell surface protein expression of mHLA-DR in blood; 3) comparative factor: none; 4) outcomes to be predicted: mortality, secondary infections, length of stay, and organ dysfunction score (sequential organ failure assessment [SOFA], multiple organ dysfunction score [MODS], logistic organ dysfunction score [LODS]), composite outcomes where component endpoints consist of at least one of the outcomes stated above (e.g., "adverse outcome" defined as death or secondary infection), 5) timing (of the prediction horizon and the moment of prognosis): any; and 6) setting: ICU.**
Condition being studied: **Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to severe infections. It can further progress to septic shock, which includes hemodynamic failure and increased mortality rates. A recent worldwide epidemiological study estimated 48.9 million sepsis cases and 11 million of sepsis-related deaths (~20% of global deaths in 2017). Although its management has advanced considerably, sepsis remains deadly and challenging to treat. The 28/30-day mortality averages around 25% for sepsis and 38% for septic shock in high-income countries. Current models describe the underlying pathophysiologic mechanisms of sepsis as an interplay between concurrent dysfunctional pro- and anti-inflammatory immune response.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 November 2022 and was last updated on 9 March 2026 (registration number INPLASY2022110119).

INTRODUCTION

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blood; 3) comparative factor: none; 4) outcomes to be predicted: mortality, secondary infections, length of stay, and organ dysfunction score (sequential organ failure assessment [SOFA], multiple organ dysfunction score [MODS], logistic organ dysfunction score [LODS]), composite outcomes where component endpoints consist of at least one of the outcomes stated above (e.g., "adverse outcome" defined as death or secondary infection), 5) timing (of the prediction horizon and the moment of prognosis): any; and 6) setting: ICU.

Rationale: Reduced monocytic human leukocyte antigen DR expression (mHLA-DR) indicates immunosuppression in intensive care unit (ICU) patients with sepsis / septic shock. Several studies suggest its association with clinical outcomes such as mortality and secondary infections, but evidence is inconsistent. This protocol for systematic reviews and meta-analyses aim to summarize and assess the current evidence on the association of mHLA-DR with mortality, secondary infections, length of stay, organ dysfunction scores, and composite outcomes (including at least one of the aforementioned endpoints) in adult patients with sepsis and septic shock.

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METHODS

Search strategy: Literature search will be conducted on Pubmed and Embase databases and Clinicaltrials.gov registry. Additional search will be performed among citations referenced in relevant scientific literature identified in the database and clinical trials registry searches.

Pubmed search terms :

1. (sepsis OR septic shock) AND HLA-DR AND (Cohort studies/ OR Incidence OR Mortality/ OR Secondary Infections/ OR Nosocomial infections/ OR Follow-up studies/ OR prognos* OR predict* OR course OR Survival analysis/)
2. ("Humans"[Mesh]) AND (("Sepsis"[Mesh]) OR ("Shock, Septic"[Mesh])) AND "HLA-DR Antigens" [Mesh]
3. ((sepsis) OR (septic shock) OR (septic patients)) AND ((mHLA-DR) OR (HLA-DR) OR (monocytic human leukocyte antigen DR) OR (human leukocyte antigen DR)) with "English", "Adult", and "Human" as filters
4. ("Humans") AND (("Sepsis") OR ("Shock, Septic")) AND "HLA-DR Antigens"
5. ((HLA DR) AND (Sepsis)) AND (immunosuppression)
6. "sepsis-induced immuno*" AND biomarker
7. "sepsis-associated immuno*" AND biomarker

Embase search terms:

1. 'human'/exp AND ('septic shock'/exp OR 'sepsis'/exp) AND 'hla dr antigen'/exp AND ('case control study'/de OR 'clinical article'/de OR 'clinical trial'/de OR 'clinical trial topic'/de OR 'cohort analysis'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'cross sectional study'/de OR 'diagnostic test accuracy study'/de OR 'exploratory research'/de OR 'human experiment'/de OR 'intermethod comparison'/de OR 'longitudinal study'/de OR 'major clinical study'/de OR 'meta analysis topic'/de OR 'methodology'/de OR 'multicenter study'/de OR 'multicenter study topic'/de OR 'observational study'/de OR 'pilot study'/de OR 'prospective study'/de OR 'retrospective study'/de OR 'systematic review'/de OR 'validation process'/de) AND ('article'/it OR 'article in

press'/it OR 'chapter'/it OR 'letter'/it OR 'review'/it)
2. ('sepsis'/exp OR 'abdominal sepsis' OR 'focal sepsis' OR 'intraabdominal sepsis' OR 'sepsis' OR 'sepsis syndrome' OR 'septic disease' OR 'septic shock'/exp OR 'sepsis-associated hypotension' OR 'septic shock' OR 'septicaemic shock' OR 'septicemic shock' OR 'shock, septic') AND 'hla dr antigen'/exp AND ('mortality'/exp OR 'mortality' OR 'mortality model' OR 'secondary infection'/exp OR 'secondary infection' OR 'secondary infections' OR 'hospital infection'/exp OR 'hospital acquired infection' OR 'hospital associated infection' OR 'hospital infection' OR 'infection, hospital' OR 'infection, nursery ward' OR 'nosocomial infection' OR 'nursery ward infection' OR 'ward infection' OR 'length of stay'/exp OR 'length of stay' OR 'sofa'/exp)
3. ('sepsis'/exp OR 'sepsis' OR 'septic shock'/exp OR 'septic shock') AND 'hla-dr' AND ('cohort studies/'/exp OR 'cohort studies/' OR 'incidence'/exp OR 'incidence' OR 'mortality/'/exp OR 'mortality/' OR 'secondary infections/'/exp OR 'secondary infections/' OR 'nosocomial infections/' OR 'follow-up studies/'/exp OR 'follow-up studies/' OR 'prognos*' OR 'predict*' OR 'course' OR 'survival analysis/'/exp OR 'survival analysis/') AND ('case control study'/de OR 'clinical article'/de OR 'clinical trial'/de OR 'clinical trial topic'/de OR 'cohort analysis'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'diagnostic test accuracy study'/de OR 'human'/de OR 'intermethod comparison'/de OR 'longitudinal study'/de OR 'major clinical study'/de OR 'meta analysis'/de OR 'methodology'/de OR 'multicenter study'/de OR 'multicenter study topic'/de OR 'normal human'/de OR 'observational study'/de OR 'open study'/de OR 'pilot study'/de OR 'proportional hazards model'/de OR 'prospective study'/de OR 'retrospective study'/de OR 'systematic review'/de) AND ('article'/it OR 'article in press'/it OR 'chapter'/it OR 'letter'/it OR 'review'/it)
4. ('sepsis'/exp OR 'sepsis' OR 'septic shock'/exp OR 'septic shock') AND ('mhla-dr' OR 'hla-dr' OR 'monocytic human leukocyte antigen dr' OR 'human leukocyte antigen dr') AND ([article]/lim OR [article in press]/lim OR [letter]/lim OR [review]/lim) AND [humans]/lim AND [english]/lim AND [clinical study]/lim
5. 'sepsis-induced immuno*' AND ('biomarker'/exp OR biomarker)
6. 'sepsis-associated immuno*' AND ('biomarker'/exp OR biomarker)
Clinicaltrials.gov registry search terms:
1) Condition or disease: sepsis; other terms: immunosuppression; study type: any; eligibility criteria: adult, older adult
2) Condition or disease: septic shock; other terms: immunosuppression; study type: any; eligibility criteria: adult, older adult
3) Condition or disease: critically ill; other terms: immunosuppression; study type: any; eligibility criteria: adult, older adult
4) Condition or disease: sepsis; other terms: HLA-DR; study type: any; eligibility criteria: adult, older adult
5) Condition or disease: septic shock; other terms: HLA-DR; study type: any; eligibility criteria: adult, older adult
6) Condition or disease: critically ill; other terms: HLA-DR; study type: any; eligibility criteria: adult, older adult
7) Condition or disease: COVID-19; other terms: HLA-DR; study type: observational; eligibility criteria: adult, older adult.

Participant or population: Adult (≥18 years old) critically ill patients with sepsis or septic shock (any type of infection and sepsis definition). Studies with subset(s) of eligible participants can be included only if data from the eligible participants can be retrieved.

Intervention: Prognostic factor: monocytic human leukocyte antigen DR (mHLA-DR) quantified as cell surface protein expression in blood as percentage of mHLA-DR positive cells, mean fluorescent intensity (MFI), or antibodies per cell (Ab/C) and reported as a continuous or categorical variable (at any cut off).

Comparator: Non applicable.

Study designs to be included: Any observational (prospective or retrospective)

clinical study reporting the outcomes of interest in relation to mHLA-DR.

Eligibility criteria: Additional exclusion criteria (not defined in the PICOS sections): 1) studies published only as conference abstracts, 2) studies in other language than English, 3) postmortem studies, 4) retracted studies, 5) old versions of reports (i.e., an updated report on the study results has been identified during search), 6) non clinical studies and records (e.g., in vitro and animal studies, study protocols, editorials, reviews, commentaries), 7) studies that used mHLA-DR threshold value as patient inclusion/exclusion criteria, 8) studies explicitly and clearly including patients with pre-existent immunosuppression due to disease/ condition or/and medication.

Information sources: Pubmed and Embase databases, clinical trial registry Clinicaltrials.gov, and screening citations referenced in relevant scientific literature identified in the database and clinical trials registry searches.

Main outcome(s): 28/30-day all-cause mortality.

Additional outcome(s): 1. mortality at any follow up
2. secondary infections at any follow up, confirmed or suspected
3. organ dysfunction score at any follow up (such as sequential organ failure score [SOFA] or multiple organ dysfunction score [MODS] or logistic organ dysfunction score [LODS])
4. length of stay (LoS) in ICU or hospital
5. composite outcomes where component endpoint consist of at least one of the outcomes stated above at any follow up.

Data management: Two review authors will independently extract study/patient characteristics and prognostic factor and outcome data using standardized data extraction forms.
Study characteristics include study design, setting, dates, inclusion/exclusion/ stratification criteria, sample size, definition of start point.
Patient characteristics include average/ median age, ratio of female and male patients, average/median admission clinical scores such as acute physiology and chronic health evaluation II (APACHE II) or simplified acute physiology score II (SAPS II), average/median admission organ dysfunction scores such as SOFA, MODS, or LODS, mortality and its' follow up, percentage of patients with secondary infections, percentage of patients with septic shock.
Data on the prognostic factor and its' association with the outcomes of interest include:
1. timing of mHLA-DR sampling, outcome follow up, and number of patients with available mHLA-DR/outcome data
2. summary data on mHLA-DR levels for patients who experienced different outcome states (e.g., survivors vs non survivors) reported as means with standard deviation (SD), standard error (SE), or 95% confidence interval (CI) or medians with interquartile range (IQR) or range, and/or p values
3. results of uni- and multivariate analysis: adjusted and unadjusted odds ratio (OR) or hazard ratio (HR) with 95% CI or SE, and/or p values
4. characteristics of ROC analysis: cut off value, area under the curve (AUC) with 95% CI and p value, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likehood ratio (LR+), and negative likehood ratio (LR-)
5. correlation coefficients with 95% CI and p values
6. qualitative description of the association if no other data are reported.
Incompletely reported data will be estimated from available information whenever possible (e.g., SD calculated from p value, see data synthesis for more detail). When such estimation is not impossible, attempts will be made to obtain the missing data from the authors.

Quality assessment / Risk of bias analysis: Risk of bias will be independently appraised by two review authors using the Quality in Prognosis Studies tool (QUIPS) for prognostic studies. Differences will be

resolved by discussion or, if required, by the third review author. Publication bias will be assessed by visual inspection of funnel plots, if at least 10 studies are available.

Strategy of data synthesis: We plan to pull data separately for adjusted and unadjusted analyses, according to measure of association used (e.g., hazard ratios separately from odd ratios), and mHLA-DR measurement time point. Grouping according to mHLA-DR sampling time will be based on the time points available in the included studies. To reduce the potential bias, it will be performed blindly, i.e., knowing the time points used in the studies but not the corresponding mHLA-DR data. We plan to have at least two groups: mHLA-DR measured at baseline and at a later time point.
If appropriate, we will combine data in meta-analysis using random-effects model (Review Manager software 5.4.1, Cochrane Collaboration, 2020), since we expect high heterogeneity between studies. If needed, means and standard deviation (SD) will be estimated from medians and interquartile range or/and range. If only p value is available, SD will be calculated from it (when no exact p value is reported, we will use its reported significance threshold e.g., 0.05). Heterogeneity of data will be evaluated using I2 statistic and Chi2 test, interpreted according to the magnitude of I2 and p value of Chi2 test.
We will apply GRADE framework adapted to prognosis research to assess out overall confidence in the results.

Subgroup analysis: Subgroup analysis will explore the impact of risk of bias.

Sensitivity analysis: We will conduct sensitivity analysis restricting evidence to studies that:
1. used standardized mHLA-DR quantification method (Ab/C)
2. used current sepsis definition (Sepsis-3)
3. did not include COVID-19 patients only
4. included septic shock patients only
5. explicitly and clearly excluded patients with pre-existing immunosuppression due to diseases/conditions or/and medication

In addition, we will check the effect of data conversion/estimation (if applied).

Country(ies) involved: Switzerland.

Keywords: mHLA-DR; Sepsis; Sepsis-associated immunosuppression; Biomarkers; Critical illness; Immune function; Immunomodulation; Immune modulation; Immune suppression; HLA-DR expression.

Contributions of each author:
Author 1 - Jan Waskowski.
Author 2 - Robin Moolan-Vadackumchery.
Author 3 - Joerg C. Schefold.

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