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PROTOCOL

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Sex differences in pediatric sepsis—a systematic review protocol

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Abstract

Background Pediatric sepsis remains a leading cause of childhood morbidity and mortality worldwide. Despite advancements in modern medicine, it accounts for more than 3 million childhood deaths per year. Multiple studies have emphasized that sex and gender have an impact on the treatment and outcome of various diseases. Adult studies have revealed sex differences in pathophysiological responses to septic shock, as well as a possible protective effect of estrogens on critical illness. Sex-specific maturational and developmental differences in host immunology have been previously demonstrated for neonatal and pediatric age groups. At present, there are no studies assessing the impact of sex on outcomes of children with sepsis.

Methods The goal of this study is to assess sex-specific differences in childhood sepsis survival outcomes. We will systematically assess associations of sex and gender with outcomes in pediatric sepsis in the literature by performing a systematic search of MEDLINE and Embase databases. We will include all English language randomized trials and cohort studies. The study population will include children > 37 weeks gestational age and < 18 years of age. Exposure will be sepsis, severe sepsis, and septic shock and the main comparison will be between male and female sex. The primary outcome will be hospital mortality. Secondary outcomes will be the pediatric intensive care unit and hospital length of stay.

Discussion Results from this review are expected to provide important information on the association of sex with the outcomes of pediatric sepsis. If an association is noted, this study may serve as a foundation for further research evaluating the pathophysiological aspects as well as potential socioeconomic factors responsible for the clinically detected sex differences.

Systematic review registration PROSPERO CRD42022315753.

Keywords Sepsis, Septic shock, Sex and gender, Childhood, Pediatric

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Introduction

Rationale

Pediatric sepsis is defined as a dysregulated host response to infection leading to life-threatening organ dysfunction and has been declared a global priority of health by the World Health Organization (WHO) [1]. Despite advances in modern medicine, pediatric sepsis remains a major contributor to mortality and morbidity worldwide, with more than 3 million children progressing to life-threatening organ dysfunction and death annually [2–6]. A recently published prospective study on sepsis outcomes in a Swiss population-based cohort showed a mortality rate of 7% in the overall pediatric population, increasing to 17% in those with septic shock [7]. This study group also demonstrated differences in outcomes according to age groups, comorbidities, and pathogen [7]. The majority of deaths occurred within 48 h after admission [8].

In sex and gender medicine, sex differences relate to differences in sexual hormones, in sex chromosomes and sex-specific gene expression from autosomes [9]. Biological sex is usually assigned at birth and based on the appearance of the external genitalia. Gender is a socially constructed definition, which encompasses cultural aspects, whereas sex is a biological categorization [10, 11]. Sex and gender differences can affect outcomes through multiple mechanisms, such as socioeconomic differences, differences in biological vulnerability or differences in biological response to treatment. For example, adult studies revealed sex differences in pathophysiological responses to septic shock [12], including the response to corticosteroid treatment, as well as a possible protective effect of estrogens on critical illness [13]. In addition, women with sepsis have been found to receive less timely initiation of antibiotics [14, 15].

Despite known sex-specific differences in the immunological response and the maturation of host defenses, which vary during childhood and adolescence [16], there is limited literature in this field related to sepsis. So far there is no data on sex differences in sepsis mortality in pediatric age groups. Considering the major hormonal and physiological changes during childhood development, there is a strong rationale to investigate the association of sex by age groups with sepsis severity and outcome.

Objectives

Our primary objective is to assess the association of sex/gender with hospital mortality in children by performing a systematic review and meta-analysis. Secondary objectives are to determine the association of sex/gender with PICU and hospital lengths of stay.

Hypothesis

This is a hypothesis-generating study investigating the association of sex with outcomes of pediatric sepsis.

Methods

We will conduct a systematic review and meta-analysis on the association of sex/gender with mortality in the pediatric sepsis population. This review protocol will follow the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines [17] and was submitted for registration in the International Prospective Register of Systematic Reviews (PROSPERO) [18]. As this is a systematic review of the literature, no ethics approval will be required.

We are aware that even though most studies report on sex or gender differences, they actually report on biological or reported sex as opposed to gender as defined above. We will therefore summarize our findings under the term "sex" which will reflect sex differences and will not specifically evaluate for gender differences. We will report on the number of studies using each term (sex and gender) and whether or not they justified the use of the reported term.

Eligibility criteria

We will include prospective and retrospective cohort studies, case–control studies, and randomized trials published in English during a 17-year period (1st January 2005–31st December 2021). We have limited our review to English language studies based on previous sepsis reviews showing that this strategy resulted in the omission of only 0.4% of studies [19].

We chose this time frame due to the publication of the International Pediatric Sepsis Definition Consensus Conference statement in 2005 [20]. This will allow sepsis definitions to be more consistent for data collection and is aligned with other sepsis reviews [19]. We will exclude systematic reviews, abstracts, case reports, and narrative reviews from our study. We will only include studies that provide mortality outcomes according to sex. We will screen references of included studies to ensure no relevant publications are missed for analysis.

The study question was defined based on CHARMS (checklist for critical appraisal and data extraction for systematic reviews of prediction modeling studies) [21].

Population

Our study population will include children $\geq$ 37 weeks post gestational age to < 18 years of age diagnosed with sepsis, severe sepsis, or septic shock (see sepsis definitions [19]) admitted to a pediatric intensive care unit (PICU), intensive care unit (ICU) or with an explicit

diagnosis of organ dysfunction. In order to conduct a pragmatic and inclusive systematic review, studies with the terms sepsis, severe sepsis, and septic shock will be included independent of the classification system used (IPSCC 2005, Sepsis-3, WHO definition, Sepsis-1, and Sepsis-2 definitions). If patients are diagnosed with sepsis and hospitalized in the ICU, we assume that the infection was severe enough to meet the previously mentioned sepsis criteria [20]. However, we will also include studies that were conducted in a setting without a PICU, if the criteria for sepsis with organ dysfunction were met.

If study data allows, we will divide patients into age groups (infants (31 days–12 months), toddlers (1–5 years), school age (5–12 years), adolescents (12–18 years)), which will be evaluated for sex-differences per age group. We will exclude premature infants and studies including neonates (0–30 days) as the main population from our analysis, as admission to the ICU in this group may be more reflective of gestational age than the severity of infection. In addition, preterm infants and newborns who have never left the hospital represent patient groups of different vulnerability, epidemiology, and outcomes, compared to the other pediatric age groups. Studies of all sepsis pathogens (viruses, fungi, parasites, bacteria etc.) and of children with inconclusive microbiological findings will be included. We will include only studies which provide analyses or reporting according to sex. Studies on exclusively adult patients or adult studies in which the pediatric data is not separately reported will be excluded.

Index comparator

The main comparison will be between male and female sex.

Outcomes

The primary outcome will be hospital mortality. Secondary outcomes will be PICU and hospital length of stay (LOS).

Data sources

We will identify eligible studies by searching the following databases: MEDLINE and Embase.

We will perform a hand search of references of the primary studies and systematic reviews for relevant grey literature studies to be included in our analysis.

Search strategy

We have developed a search strategy with the help of an information specialist from the University Library Zurich. The following search terms were used: "sepsis, severe sepsis, septic shock, child, pediatric, mortality". The detailed search strategy is outlined in the Appendix 1.

Study selection and screening process

The titles found in the primary search will be screened with the help of a web-based systematic review platform (Covidence). Citations will be screened for eligibility based on title, abstract, and full text. Screening of citations at each level will be performed by two independent reviewers. Conflicts will be resolved by a third reviewer. Titles rejected by both reviewers will be excluded and the remaining titles will undergo full text screening. Each full-text article will be screened by two investigators for inclusion in the final dataset, which will then undergo data extraction. Conflicts will be resolved by a third reviewer. Kappa scores on the level of agreement reached between the reviewers at each stage of screening will be calculated and reported. We will document the rationale for the inclusion and exclusion of studies.

Data extraction and management

Data from included full-text articles will be extracted by two reviewers and inserted into an electronic case report form (eCRF) in Redcap.

Data items

Data extraction will include information related to study characteristics (title, authors, year of publication, country, journal, study design, sample size, and inclusion/exclusion criteria); population characteristics (age, sex, ethnicity, admission diagnosis, location of the admission within the hospital), exposure (sepsis, severe sepsis, septic shock), covariates (comorbidities: chronic neurological, respiratory or cardiac disorders, oncology, and transplant patients, type of infection, the severity of illness scores (Pediatric Index of Mortality II [22], PRISM [23] at admission); and outcomes (hospital mortality, PICU and hospital LOS). If needed, the authors of the original articles will be contacted to obtain missing data.

Assessment of quality and risk of *bias* in included studies

Since this analysis is based on existing research, publication bias is possible when performing a systematic review. Selection bias will be addressed with a systematic and reproducible search by an information specialist. References in included studies will be screened to further reduce the risk of selection bias.

All included studies will be evaluated with respect to their risk of different biases (e.g., selection, attrition, detection bias) according to study design. We will assess the quality in selected studies using the Quality in Prognosis Studies (QUIPS) tool for assessment of risk of bias [24]. Risk of bias assessment will

be reported as "low risk", "intermediate risk" or "high risk". The risk of bias will be assessed by two independent raters, and discrepancies will be resolved by involving a third party.

A subgroup analysis will be performed to assess for a subgroup effect. Should this be the case, we will perform a separate sensitivity analysis for high ROB Studies.

Data synthesis and analysis

Statistical methods will include study-level descriptive statistics of the studies included in the systematic review. It is anticipated that the majority of included studies will not be focused on sex as a prognostic factor for mortality in sepsis but will instead simply report sex proportions in those who did and did not survive. As such, our analysis will simply be to determine if there is an association between sex and mortality in pediatric sepsis and will serve as a basis for future prognostic models. Forest plots will be used to visualize the primary and secondary outcomes across studies. If the same secondary outcome is reported in two or more studies or study arms, a meta-analysis will be calculated with a random effects model as we anticipate substantial heterogeneity between studies. If possible, meta-regression models will be fitted to quantify the association between covariates and the primary and secondary outcomes. Funnel plots will be shown to address reporting/publication bias if at least ten studies report on the primary outcome. Depending on the outcome distribution, different effect measures will be meta-analyzed: proportions for in-hospital mortality (and PICU), and mean or median durations for hospital LOS. Statistical heterogeneity will be reported by an I^2-statistic and Cochrane's Q.

We will provide a narrative synthesis of our results if statistical analysis is not possible due to a low number of studies or heterogeneous outcomes. If four or more studies report a given covariate, we will perform subgroup analysis by age, congenital disease or any other non-congenital major comorbidity (such as oncological diagnosis), ethnicity, type of infection, severity of illness scores (Pediatric Index of Mortality II [22], PRISM [23] score) at admission. A sensitivity analysis will be conducted for the primary outcome, including all studies that have been rated as low risk of bias.

Discussion

Pediatric sepsis is a socioeconomically and medically highly relevant disease on a global level with an estimated mortality of 3 million deaths annually [2–6]. This work will be the first systematic review specifically analyzing potential sex differences in the field of pediatric sepsis. Results from this review are expected to provide important information on the influence of sex differences on the outcomes of pediatric sepsis. This study may serve as a foundation for further research evaluating the pathophysiological aspects as well as the socioeconomic factors responsible for the clinically detected sex differences. In the future, diagnostic and therapeutic strategies might have to be tailored to more individualized patient characteristics in order to improve outcomes.

An important limitation of this study will be the inability to differentiate between biological (e.g., hormonal) or socioeconomic factors possibly contributing to assessed sex/gender differences. In addition, we are including only studies in the English language, which might exclude relevant studies in other languages. We are aware of the fact that the term sepsis is often variably applied in current literature, which will be a limitation for the generalizability of our results [25].

Abbreviations

eCRF	Electronic case report form
ICU	Intensive care unit
IPSCC	International Pediatric Sepsis Consensus Conference
LOS	Length of stay
NICU	Neonatal intensive care unit
PICU	Pediatric intensive care unit
PRISM	The Protocolized Resuscitation in Sepsis Meta-Analysis
ROB	Risk of bias
WHO	World Health Organization

Supplementary Information

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Supplementary Material 1: Appendix 1:Search Strategy MEDLINE.

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Authors' contributions

UK established the research idea and was involved in screening the literature, preparation, and writing of the manuscript. JM was involved in the correction of the manuscript and the performance of a preliminary literature search. LS had the role of mentor and supervisor of the project and reviewed and corrected the manuscript. KM had the role of an advisor with great experience in the performance of systematic reviews and reviewed and corrected the manuscript. JHL had the role of an advisor regarding the implementation of the systematic review and reviewed and corrected the manuscript. UH had the role of statistical advisor and support and reviewed the manuscript.

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Availability of data and materials
Access to data will be made available upon direct inquiry to the corresponding author.

Declarations

Ethics approval and consent to participate
As this is a systematic review of the literature, no ethics approval will be required.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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