Final protocol (version 02)

1. Title of the project

Clinical Utility of Biomarkers for Outcomes Prediction in Adults with Suspected Sepsis Presenting to the Emergency Department

2. Name of the Evidence Synthesis Group and project lead

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3. Plain language summary

Sepsis is a life-threatening reaction to an infection, which requires prompt treatment. It happens when a person's immune system over-responds to an infection and starts to damage their body tissues and organs. Without treatment, sepsis can worsen quickly and cause organ failure and death. Nevertheless, early signs of sepsis can be difficult to spot.

Over the past few decades, several methods have been developed to help healthcare professionals to decide if someone has sepsis and if they need to be treated quickly. These include criteria and severity scores, such as the systemic inflammatory response syndrome (SIRS) criteria, the Third International Consensus Definition for Sepsis and Septic Shock (Sepsis-3) criteria, the quick sepsis-related organ dysfunction assessment (qSOFA) score, and the updated National Early Warning Score (NEWS2). In general, these evaluate things such as the patient's blood pressure, breathing, and heart rate. Patients with higher scores need to be assessed and treated promptly. However, even with these scores, it can still be difficult to identify precisely patients who may get worse. This is because of the great variability between individuals in the signs and causes of infection, other medical conditions they may have, and how they respond to treatment. Therefore, it has been suggested that the use of biomarkers would improve the identification of patients at high risk of their sepsis worsening and help guide treatment. Biomarkers are specific cells, molecules, or genes that appear when a person has a particular health condition and can provide useful information on the condition. In sepsis, biomarkers include traditional ones, such as proteins and cytokines and some that are more novel, such as leukocyte transcriptomic markers and genetic markers. However, the role of these biomarkers in identifying patients with sepsis who are more likely to develop severe symptoms is unclear.

Therefore, we will review the current evidence on the use of biomarkers, both traditional and novel. for identifying patients who are at high risk of their sepsis worsening when they are in the hospital emergency department and have early warning signs for sepsis.

4. Background

Sepsis is defined as life-threatening organ dysfunction characterised by a dysregulated host response to infection.(1) It is considered a major public health issue worldwide due to its increasing incidence and high mortality rate.(2) The Global Burden of Sepsis study (published in 2020) reported a total of 48.9 million cases of sepsis resulting in 11 million deaths worldwide in 2017.(3) In the United Kingdom (UK) recent estimates suggest there are around 245,000 cases of sepsis a year responsible for up to 48,000 deaths.(4) Sepsis is a heterogeneous disease due to high variability between individuals in terms of microorganisms causing infection, site of infection, host response, comorbidities, and response to treatment. Early and accurate identification of individuals with suspected sepsis who are at high risk of deterioration to critical illness may enable clinicians to intervene earlier with key therapies, to rapidly escalate care where appropriate, to promptly manage any associated organ dysfunction and potentially improve patient outcomes.

Clinical risk stratification of sepsis

The 1991 International Consensus Definition Task Force (Sepsis-1) previously defined sepsis using systemic inflammatory response syndrome (SIRS) criteria (Table 1).(5) According to SIRS, a sepsis diagnosis required there to be a clinical suspicion of infection in association with the presence of at least two, of the four SIRS criteria (1. body temperature >38^{o}C or <36^{o}C; 2. heart rate >90 per minute; 3. respiratory rate >20 per minute or an arterial partial pressure of CO2 [PaCO2] of <32 mm Hg on blood gas; 4. white blood cell count <4 x 10^{9}/L or >12 x 10^{9}/L). The 2001 task force (Sepsis-2), while recognising the limitations of the sepsis definitions, did not change them, though did expand the list of diagnostic criteria (a list of possible signs of systemic inflammation in response to infection).(6)

In 2016, the Third International Consensus Definition published the Sepsis-3 definitions for sepsis and for septic shock, getting rid of the confusing term ‘severe sepsis’ and the inadequately sensitive or specific SIRS diagnostic criteria. This definition remains current and highlights the importance of identification of organ dysfunction in the diagnosis of sepsis and recommends the Sequential (Sepsis-Related) Organ Failure Assessment (SOFA) score for this purpose.(1) For patients with infection, an increase of 2 points in the SOFA score is associated with in-hospital mortality of greater than 10%.(1) Since SOFA was intended to be used in the intensive care unit, it was not clinically applicable at the time of the first hospital

assessment, and, therefore, the quick SOFA (qSOFA) score was created. This is comprised of three clinical components: systolic blood pressure (SBP), conscious level and respiratory rate, all immediately available in out-of-hospital, emergency department and hospital ward settings (Table 2).(1) qSOFA allocates 1 point each for hypotension (SBP ≤100 mm Hg); altered mental status (Glasgow Coma Score <15) and tachypnoea (respiratory rate ≥22/min). A qSOFA score of 2 or more quickly identifies patients more likely to need intensive care or to die in hospital. The Sepsis-3 clinical definition of septic shock is sepsis and persistent hypotension (mean arterial BP ≤65 mm Hg or vasopressor requirement despite adequate volume replacement) and blood lactate ≥2 mmol/L. Patients meeting these criteria have a 40% chance of in-hospital death.

As SOFA and qSOFA scores are designed to identify organ dysfunction, they are quite specific for identifying those who are sick, but sensitivity is not optimal. In the UK the second iteration of the National Early Warning Score (NEWS2) is in widespread use to give a more detailed assessment of physiological derangement, using six physiological parameters (Table 3) to give an aggregate score between 0 and 20, reflecting increasing illness severity.(7) Although NEWS2 may demonstrate superior performance to qSOFA in the determination of those at high risk of a poor outcome in undifferentiated patients, it is not specific for those with systemic infection, as it identifies many patients with pathologies that would not benefit from antibiotics. (8) Initiatives such as the Surviving Sepsis Campaign have led to the recommendation of the rapid delivery of bundles of sepsis care (including parenteral antibiotics), often when particular thresholds are breached, for example, a NEWS2 score ≥5.(9) While this may be good practice in the sickest individuals, concerns have been raised about the reflex treatment of all patients in this group and importantly, about antibiotic resistance. Consequently, the Academy of Medical Royal Colleges (AOMRC) in the UK has recently proposed a framework that outlines a more nuanced approach to antibiotic timing based on severity of illness, as described by the NEWS2 score, and clinician determination of the probability of bacterial infection.(10) Though assimilating best available evidence, it is acknowledged that there is still room for significant improvement in strategies to determine severity and prognosis amongst patients presenting with suspected sepsis.

Table 1 Systemic Inflammatory Response Syndrome (SIRS) criteria

Two or more of: • Temperature >38°C or <36°C • Heart rate >90/min • Respiratory rate >20/min or Paco2 <32 mm Hg (4.3 kPa) • White blood cell count >12,000/mm3 or <4000/mm3 or >10% immature bands

Source: Bone et al. (1992) (5)

Table 2 qSOFA (Quick Sequential Organ Failure Assessment) criteria

qSOFA (Quick SOFA)	Criteria Points
Respiratory rate ≥22/min	1
Change in mental status	1
Systolic blood pressure ≤100 mmHg	1

Source: Singer et al. (2016)(1)

Table 3 NEWS2 (National Early Warning Score 2) criteria

NEWS2 physiological parameter
1. respiration rate
2. oxygen saturation
3. systolic blood pressure
4. pulse rate
5. level of consciousness or new confusion*
6. temperature.

*The patient has new-onset confusion, disorientation and/or agitation, where previously their mental state was normal - this may be subtle. The patient may respond to questions coherently, but there is some confusion, disorientation and/or agitation. This would score 3 or 4 on the GCS (rather than the normal 5 for verbal response) and score 3 on the NEWS system.
Source: Royal College of Physicians (2017)(7)

Prognostic biomarkers

In some clinical situations, biomarkers can be used to aid the diagnosis, risk stratification and prognosis of patients presenting to the emergency department. With regard to patients with clinically suspected sepsis, the incorporation of prognostic biomarkers may greatly improve risk stratification and prove crucial for the early identification of patients at high risk of

deterioration, for guiding treatment interventions and for developing a more personalised approach to sepsis management.

Traditional markers evaluated in the context of sepsis include protein and cytokine biomarkers. Procalcitonin, C-reactive protein (CRP), lactate, interleukin 6 (IL-6), and soluble urokinase plasminogen activator receptor (suPAR) are well-studied biomarkers. Novel biomarkers include blood leukocyte transcriptomic markers and genetic markers. The existing literature does not give clear guidance about the approach to early risk stratification using prognostic biomarkers. Therefore, there is an unmet need to explore a biomarker-based risk stratification approach in patients during the initial phase of their presentation to hospital, comprising diagnosis, evaluation of severity and resuscitation.

5. Objectives

To investigate the clinical utility of traditional and novel biomarkers (assessed individually or in combination) in identifying patients at high risk of deterioration among those who present to the hospital emergency department with clinically suspected sepsis. Risk of deterioration will be assessed in terms of admissions to critical care, episodes of septic shock and organ failure and number of deaths.

Table 4 presents the review question using the PICOTS format based on CHARMS-PF, a modified version of CHARMS (CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies), which includes key items relevant to Prediction Factors studies.(11-13)

Table 4 PICOTS of the review based on CHARMS-PF (checklist for critical appraisal and data extraction for systematic reviews of prediction modelling studies and of prognostic factors studies)(11, 12)

Population targeted	Adults presenting to emergency departments with suspected sepsis
Index prognostic factor	Biomarkers assessed individually or in combination: • Procalcitonin (PCT) • C-reactive protein (CRP) • SUPAR (Soluble Urokinase-type Plasminogen Activator Receptor) • Lactate • Cytokines [GM-CSF; IFN gamma; Interleukin (IL)-1 beta; IL-2; IL-4; IL-5; IL-6; IL-8 (CXCL8); IL-10 (CXCL10); IL-12p70; IL-13; IL-17A (CTLA-8); MCP-3 (CCL7); and TNF alpha]. • Monocyte distribution width (MDW) • Blood leukocyte transcriptomic markers – eight neutrophil (cluster of differentiation antigens (CD) CD15; CD24; CD35; CD64; CD312; CD11b; CD274; CD279), seven monocyte (CD35; CD64; CD312; CD11b; HLA-DR; CD274; CD279) and a CD8 T-lymphocyte biomarker (CD279) • Genetic markers • Any other biomarkers deemed important by the reviewers
Comparator prognostic factor	• Established prognostic markers and risk stratification based on physiology and standard laboratory tests
Outcome(s) to be predicted	• Critical care admission • In-hospital or 30-day mortality • Organ failure • Septic shock
Time span of prediction	• Prognostication: On admission to Emergency Department • Outcome: All time span
Setting (intended role and use)	• To inform healthcare professionals of the risk of deterioration in patients suspected of sepsis who present at the emergency department. • To help improve risk stratification, early assessment and management of patients with sepsis.

6. Methods

Types of studies

We will consider studies of any design published in English in the last 10 years (2013-2023), which assess the value of biomarkers for the prediction of clinically relevant outcomes. We will focus on studies assessing prediction factors and not on studies assessing or validating prediction models. Conference abstracts will be excluded because they are not considered to provide sufficient information. However, if potentially relevant conference abstracts are identified, we will investigate whether fuller information is available from another source.

Targeted population

We will include studies that focus on adults presenting to the emergency department with clinically suspected sepsis. To be eligible, studies must have conducted the analysis in a population with clinically suspected sepsis. We will exclude studies that recruited the suspected sepsis population, but clearly limit the prognostic factor analysis to patients with confirmed sepsis by excluding non-sepsis patients. Where there is ambiguity regarding whether the study population had clinically suspected sepsis or confirmed sepsis, the reviewers will seek clinical expert opinion and achieve consensus on study's eligibility. We will record the definition of suspected and confirmed sepsis used by the study authors.

We will accept the definition of 'adults' as reported by the authors of the included studies. Studies that assess patients with post-operative or hospital-acquired infection or those with trauma or burn injury will not be deemed suitable for inclusion. Studies including a mixed population will be considered for inclusion if most patients (i.e., 80%) meet the pre-specified eligibility criteria.

Target condition

For each included study, we will consider the criteria used by the study authors for defining the population with sepsis. We will accept criteria based on Sepsis 3 definitions (qSOFA score of 2 or more),(1) NEWS2 score of 5 or more, (7) as well as physiological definitions that are broadly equivalent to these. For studies published before 2016, we will consider the previous SIRS and Sepsis-2 criteria to be adequate (9).

Biomarkers of interest

The biomarkers of interest, assessed individually or in combination, include the following:

- Procalcitonin (PCT)
- C-reactive protein (CRP)
- Soluble Urokinase-type Plasminogen Activator Receptor (suPAR)
- Lactate
- Cytokines [Granulocyte-macrophage colony-stimulating factor (GM-CSF); interferon□gamma (IFN□γ); interleukin (IL)-1 beta; IL-2; IL-4; IL-5; IL-6; IL-8 (CXCL8); IL-10 (CXCL10); IL-12p70; IL-13; IL-17A (CTLA-8); MCP-3 (CCL7); and tumor necrosis factor alpha (TNF-α)].
- Monocyte distribution width (MDW)
- Blood leukocyte transcriptomic markers – eight neutrophil (cluster of differentiation antigens (CD) CD15; CD24; CD35; CD64; CD312; CD11b; CD274; CD279), seven monocyte (CD35; CD64; CD312; CD11b; HLA-DR; CD274; CD279) and a CD8 T-lymphocyte biomarker (CD279)
- Genetic markers
- And any other biomarkers deemed important by the reviewers.

Outcome measures

Outcomes of interest (see Table 4) are:

- Critical care admission
- In-hospital mortality at any timepoint
- 30-day mortality
- Overall survival rate
- Organ failure
- Septic shock

Timing

The timing of biomarker measurement is considered important for the scope of this systematic review. We are primarily interested in the role of biomarkers in the assessment of patients with suspected sepsis identified within the first 12 hours upon arrival at the emergency department and not later than 24 hours. If the timing of biomarker measurement is

reported to exceed 24 hours from arrival at the emergency department, the studies will be excluded. However, to adopt a comprehensive approach, studies that report to measure biomarkers at the emergency department but do not specify the timing of measurement will be considered eligible for inclusion.

Search methods for identification of studies

A sensitive literature search strategy will be developed by an Information Specialist to identify published, peer-reviewed studies. The search strategy will include database index terms and free text to encompass the facets of sepsis, selected biomarkers, the emergency department setting, and prognosis. A range of databases will be searched to include MEDLINE, Embase, the Cochrane Database of Systematic Reviews, and CENTRAL. There will be no restrictions on study type or language at the search stage, but results will be limited to publications after 2012. All references will be exported to Endnote for recording and deduplication. The reference lists of all articles selected for full-text appraisal will be screened for additional studies. Outline searches for Ovid MEDLINE and Embase are shown in Appendix 1.

Data collection

Selection of studies

One review author will screen titles and abstracts identified by the search strategies. A second author will independently screen a random sample of titles and abstracts (20%). In keeping with our embedded version of SWAR 01 (see section 7) the first review author will screen titles and abstracts simultaneously while the second author will screen the titles first and then check the abstracts for those that they deem potentially eligible. A single reviewer will perform an initial screen of the full-text versions of potentially relevant articles to identify studies that can be subsequently excluded based on the pre-specified inclusion/exclusion criteria. The remaining studies will be independently reviewed by two reviewers. Number of excluded studies and main reasons for exclusion will be recorded.

Data extraction

For each study, we will extract information on publication date and date the study was done, study design, demographic and baseline characteristics of participants, number, type, and definition of outcome events, and details of biomarker measurements including the

manufacturer of the biomarker assay (based on the CHARMS-PF checklist). Data will be extracted by one reviewer using a bespoke data extraction form and verified by a second reviewer.

Risk of bias assessment

We will use the QUIPS (Quality in Prognostic Factor Studies) tool to assess the methodological quality of included studies.(14) The QUIPS tool includes domains on study participation, study attrition, prognostic factor measurement, outcome measurement, adjustment for other prognostic factors, and statistical analysis and reporting. Studies will be rated as "low", "moderate" or "high" risk of bias. We will not exclude studies rated at high risk of bias, but we will consider them to be less reliable than low or medium risk of bias studies when synthesising the evidence. Risk of bias will be assessed by one reviewer and verified by a second reviewer.

Any disagreements between review authors regarding study selection, data collection and risk of bias assessment will be resolved by consensus or referred to a third author for adjudication.

Data synthesis

We aim at conducting a review of prognostic factor studies. From each included study, for each relevant prognostic factor, we will extract the reported **risk ratios, odds ratios or hazard ratios** and accompanying 95% confidence intervals (CIs). Where available, we will extract separate risk estimates with confounder adjustments as reported by the study authors. We will consider contacting study authors for missing data. When reported, we will also extract the **area under the receiver-operating characteristic curve (AUC)** and corresponding measures of uncertainty (95% CIs or SEs). To interpret AUC estimates, we will follow current standards that specify AUCs of less than 0.70 as poor, 0.70 to 0.79 as fair, 0.80 to 0.89 as good, and 0.90 to 1 as excellent.(15) For studies that report only an AUC, we will try to convert the AUC into corresponding odds ratio if the required assumptions are met.(16, 17) However, if the assumptions are not met, a meta-analysis of AUC values will be carried out using data from all studies that have reported AUC. AUC values and reported 95% CIs will be transformed to the logit scale and the variance of logit AUC will be calculated. Random effects meta-analyses of logit AUC and variance values will then be performed using restricted maximum likelihood (REML) estimation. The pooled logit

AUC and 95% CIs will then be back-transformed. If AUC is also not available, we will record **sensitivity and specificity** estimates.

We will record the biomarker threshold specified by the study authors. Where data are reported for multiple biomarker thresholds within a study, we will record the estimates that correspond to the best-performing value.

We will calculate summary effect estimates and their 95% CIs using the Der Simonian and Laird random-effects model, which allows for unexplained heterogeneity across studies. According to the way data are reported in the included studies, for each biomarker or combination of biomarkers we will consider separate meta-analyses for:

- Risk ratios, odd ratios, and hazard ratios
- Unadjusted and adjusted estimates
- Prognostic factors assessed at similar thresholds

The I^2-statistics will be used to describe the percentage of variation across included studies due to heterogeneity. We will use the following thresholds for the interpretation of I^2: <30% will indicate low heterogeneity, 30–60% moderate heterogeneity and >60% high heterogeneity. (18)

We will investigate the presence of publication bias in meta-analyses of prognostic factors with a visual inspection of funnel plots and the Egger's bias test.(19) Moreover, in the presence of publication bias, we may consider conducting a trim and fill adjusted analysis to impute missing studies and re-calculate the effect size. (20)

Where sufficient data are available, we will perform subgroup analyses to explore potential sources of between-study heterogeneity. Planned subgroups include:

- Patients of different age groups
- Patients with specific comorbidities
- Studies performed in the NHS versus studies not performed in the NHS
- Timing of biomarker measurement

For all analyses, the STATA software (version 18 or latest version, StataCorp, College Station, Texas) will be used.

7. Studies Within a Review (SWAR)

We will embed versions of two SWAR in this systematic review and consider a third. As noted above, we will conduct a version of SWAR 01 as part of the process to screen titles and abstracts for eligibility. One review author will screen all the records retrieved by the database searches with simultaneous access to their titles and abstracts. A second author will screen a random 20% of the retrieved records by first checking their titles and then checking the abstracts for those that are judged to be potentially eligible. We will compare the time taken to screen the records in the 20% random sample using each method and the comparative yield of eligible studies. We will also conduct a version of SWAR 06, as an observational study of the time taken to complete the various tasks in the review, including study selection, data extraction, risk of bias assessment and analysis. Finally, when the review is finished, we will consider conducting a version of SWAR 02, which would compare user understanding of different types of summaries of the review and its findings (e.g. plain language summary, scientific abstract and podcast).

8. Competing interests of authors

None

9. References

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10. Appendices

Appendix 1: Medline and EMBASE search strategy

Ovid Medline

1. Sepsis/ or Septic Shock/
2. Systemic Inflammatory Response Syndrome/
3. (sepsis or "septic shock" or SIRS or "Systemic Inflammatory Response Syndrome").tw.
4. 1 or 2 or 3
5. *Procalcitonin/ or Procalcitonin.tw.
6. *Receptors, Urokinase Plasminogen Activator/ or SUPAR.tw.
7. exp *Cytokines/ or (interleukin*, or TNF*, or IFN gamma or GM-CSF).tw.
8. *C-Reactive Protein/ or "C-reactive protein".tw.
9. exp *Phenotype/ or *Phenomics/ or (phenotype? or sub-phenotype? or subphenotype? or clinicomolecular or metabolic? or metabolomic?).tw.
10. Gene expression profiling/
11. exp Genetic structures/
12. transcriptome.tw.
13. ("monocyte distribution width" or MDW).tw.
14. lactate.tw.
15. (CD15 or CD24 or CD35 or CD64 or CD312 or CD11b or CD274 or CD279 or CD35 or CD64 or CD312 or CD11b or HLA-DR or CD274 or CD279).tw.
16. or/5-15
17. Emergency Service, Hospital/
18. (emergency adj5 (room? or service? or department? or ward? or admit* or admission? or triage or care or hospital? or physician?)).tw.
19. 17 or 18
20. exp mortality/ or follow up studies/
21. exp risk/
22. exp cohort studies/
23. exp prognosis/
24. exp incidence/
25. exp survival analysis/

26. (prognos* or outcome? or predict* or risk or cohort or incidence or survival or causal factors or course).tw.
27. or/20-26
28. 4 and 16 and 19 and 27
29. limit 28 to yr="2013 -Current"

Ovid Embase

1. sepsis/ or septic shock/
2. systemic inflammatory response syndrome/
3. (sepsis or "septic shock" or SIRS or "Systemic Inflammatory Response Syndrome").tw.
4. 1 or 2 or 3
5. *Procalcitonin/ or Procalcitonin.tw.
6. urokinase receptor/ or SUPAR.tw.
7. exp *cytokine/ or (interleukin*, or TNF*, or IFN gamma or GM-CSF).tw.
8. *C-Reactive Protein/ or "C-reactive protein".tw.
9. exp *Phenotype/ or *Phenomics/ or (phenotype? or sub-phenotype? or subphenotype? or clinicomolecular or metabolic? or metabolomic?).tw.
10. gene expression profiling/
11. exp gene structure/
12. transcriptome.tw.
13. ("monocyte distribution width" or MDW).tw.
14. lactate.tw.
15. (CD15 or CD24 or CD35 or CD64 or CD312 or CD11b or CD274 or CD279 or CD35 or CD64 or CD312 or CD11b or HLA-DR or CD274 or CD279).tw.
16. or/5-15
17. emergency ward/
18. (emergency adj5 (room? or service? or department? or ward? or admit* or admission? or triage or care or hospital? or physician?)).tw.
19. 17 or 18
20. mortality/ or follow up/
21. risk/
22. cohort analysis/
23. prognosis/

24. exp incidence/
25. survival analysis/
26. (prognos* or outcome? or predict* or risk or cohort or incidence or survival or causal factors or course).tw.
27. or/20-26
28. 4 and 16 and 19 and 27
29. conference abstract.pt.
30. 28 not 29
31. limit 30 to yr="2013 -Current"