

BMJ Open Diagnostic and prognostic accuracy of Protein C in adult patients with sepsis: protocol for a systematic review and meta-analysis

Vanessa Catenacci,¹ Fatima Sheikh,² Kush Patel,³ Alison Fox-Robichaud ⁴

To cite: Catenacci V, Sheikh F, Patel K, *et al*. Diagnostic and prognostic accuracy of Protein C in adult patients with sepsis: protocol for a systematic review and meta-analysis. *BMJ Open* 2021;**11**:e050754. doi:10.1136/bmjopen-2021-050754

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2021-050754>).

Received 27 February 2021
Accepted 18 August 2021



© Author(s) (or their employer(s)) 2021. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

¹Biochemistry, McMaster University Faculty of Science, Hamilton, Canada

²Department of Health Research Methods Evidence and Impact, McMaster University Faculty of Health Sciences, Hamilton, Canada

³Biochemistry and Biomedical Sciences, McMaster University Faculty of Health Sciences, Hamilton, Canada

⁴Medicine, McMaster University Faculty of Health Sciences, Hamilton, Canada

Correspondence to

Dr Alison Fox-Robichaud;
afoxrob@mcmaster.ca

ABSTRACT

Introduction Sepsis is a dysregulated host response to infection characterised by activation of proinflammatory and procoagulant mechanisms. Protein C (PC)'s activity as an anticoagulant and antiinflammatory molecule makes it an appealing target for sepsis biomarker studies. To date, there has been no systematic review of PC as a sepsis biomarker.

Objectives To evaluate the diagnostic accuracy and prognostic strength of PC as a biomarker for adult sepsis.

Methods and analysis Medline, Embase, Cochrane Library, PubMed and Cumulative Index to Nursing and Allied Health Literature (CINAHL) will be searched from inception through 20 January 2021 for prospective observational studies that evaluate the use of PC as a diagnostic or prognostic biomarker for adult sepsis. Title and abstract screening, full-text screening and data extraction will be conducted in duplicate. Risk of bias will be assessed using the Quality Assessment of Diagnostic Accuracy Studies and Quality in Prognostic Studies tools. If sufficient data are available, a meta-analysis will be conducted. The standardised mean difference and 95% CI will be calculated for prognostic and diagnostic studies. If possible, a hierarchical summary receiver operator characteristic curve will be generated to assess overall prognostic and diagnostic biomarker accuracy. I^2 statistics will be used to assess heterogeneity. Sensitivity analysis will be performed by removing studies with a high risk of bias and re-examining the meta-analysis results.

Ethics and dissemination Given this is a systematic review and meta-analysis, there is no requirement for ethics approval. Findings will be disseminated through a peer-reviewed publication and social media.

PROSPERO registration number CRD42021229786.

INTRODUCTION

Rationale

Sepsis is defined by Singer *et al* as 'life-threatening organ dysfunction caused by a dysregulated host response to infection'.¹ Site of infection, type of infective microorganism and patient characteristics are factors that contribute to the variable presentation of sepsis.² Despite differences in clinical phenotypes, sepsis pathology displays procoagulant,

Strengths and limitations of this study

- This is the first systematic review and meta-analysis to evaluate Protein C's biomarker potential in adult patients with sepsis and has the possibility of informing future clinical practice
- The risk of bias in included studies will be assessed using the Quality in Prognostic Studies or Quality Assessment of Diagnostic Accuracy Studies specifically developed to assess the risk of bias in prognostic and diagnostic studies, respectively.
- The search criteria may miss unpublished articles and preliminary results of ongoing studies.
- There may be challenges with meta-analysis due to the heterogeneity in the primary studies; however, this heterogeneity will be addressed through sensitivity analysis.
- There may be limited publications using current sepsis definitions.

proinflammatory and antifibrinolytic characteristics that contribute to the clearance of infection and organ recovery.³ Cytokine production by innate immune cells is stimulated by the presence of foreign antigens. This results in the upregulation of endothelial adhesion molecules, activation of the complement system and increased leucocyte proliferation.⁴ This excessive immune response stimulates the release of tissue factor by monocytes and endothelial cells, leading to activation of the extrinsic coagulation cascade.⁵ Although coagulation and subsequent fibrin deposition are essential host-defence mechanisms, excessive activity can lead to microvascular thrombosis and organ dysfunction.⁵ This causes inflammation and ischaemia, leading to tissue hypoxia, haemodynamic instability, multiorgan failure and death.⁶

Globally, the sepsis case fatality rate is approximately 25%, with a 2017 study estimating 48.9 million incident cases of sepsis and 11 million sepsis-related deaths

annually.⁷ While the *Surviving Sepsis* campaign emphasises the importance of early therapeutic intervention, diagnosing the condition, due to variable pathology, is a major impediment to early treatment.⁸ While the current Sepsis-3 definition uses the Sequential Organ Failure Assessment (SOFA) scale to diagnose patients, the use of a highly specific and sensitive diagnostic biomarker could aid timely and appropriate antibiotic therapy. In addition, SOFA and quick SOFA (qSOFA) are also used to identify septic patients high-risk for mortality. However, SOFA is limited by low specificity, and qSOFA sensitivity and specificity are shown to vary widely across studies.^{9–11} There is also no consensus on a specific biomarker that can distinguish patients high-risk for mortality.

Biomarkers are an appealing research target for sepsis because their rapid quantification has the potential to diagnose disease, predict prognosis and guide early therapeutic interventions. While over 250 biomarkers for sepsis are described in the literature, few are used in clinical practice due to low sensitivity and specificity.¹² Given the complex intersection between inflammation and coagulation in sepsis pathology, an ideal sepsis biomarker would intersect both these pathways. One such example is Protein C (PC). Also referred to as auto-prothrombin IIA, PC is a vitamin K-dependent glycoprotein that circulates through the blood plasma.¹³ PC is the zymogen of activated PC (aPC), a serine protease involved in regulating host defence systems through anticoagulant, antiapoptotic and anti-inflammatory properties.¹⁴ Previous research demonstrated that PC levels are significantly lower in patients with sepsis compared with healthy controls.¹³ Decreases in endogenous PC during sepsis are attributed to increased conversion to aPC, decreased protein synthesis in the liver, and degradation by neutrophil elastase.^{15–17} To date, the use of PC as a biomarker for sepsis has only been reported in individual clinical studies. Therefore, to identify the potential clinical application of PC as a biomarker for sepsis, this systematic review and meta-analysis will synthesise existing knowledge and evaluate its utility as a prognostic and diagnostic biomarker.

The overall aim of the proposed systematic review and meta-analysis is to synthesise and evaluate existing knowledge on the utility/use of PC as a biomarker for adult sepsis.

Objectives

1. To determine the diagnostic accuracy of PC as an independent biomarker for sepsis.
2. To determine the prognostic strength of PC as an independent biomarker of mortality in septic patients.

METHODS

This systematic review protocol follows the reporting guidelines established by the 2015 Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P).¹⁸ The protocol for this study was registered

on the international register of systematic reviews (PROSPERO CRD42021229786).

Eligibility criteria

Type of studies

This systematic review aims to include all published prospective observational studies that examine PC as a diagnostic marker of sepsis or as a prognostic marker for mortality in patients with sepsis. Retrospective observational studies, abstracts, editorials, poster presentations and non-English studies will be excluded. There will be no restrictions on study quality, date, setting or size.

Types of participants

The population of interest includes male and female adults (>17 years of age) with sepsis (including severe sepsis, septic shock or sepsis with disseminated intravascular coagulation (DIC)) or suspicion of sepsis. Studies that only include patients with confirmed sepsis will be used to evaluate the prognostic accuracy of PC, while studies that included patients with sepsis or suspicion of sepsis will be used to assess the diagnostic accuracy of PC. Paediatric studies (<17 years of age) and animal studies will be excluded to reduce heterogeneity within patient populations. Suspicion of sepsis will be defined as evidence of infection or organ dysfunction.¹⁹ Studies that used the following gold standard sepsis definitions will be included:

1. Sepsis-1: established by the American College of Chest Physicians and Society of Critical Care Medicine in 1991.²⁰
2. Sepsis-2: established by the Society of Critical Care Medicine, European Society of Intensive Care Medicine, American College of Chest Physicians, American Thoracic Society, and Surgical Infection Society in 2001.²¹
3. Sepsis-3: established by the Society of Critical Care Medicine and European Society of Intensive Care Medicine in 2016.²²

Given the constantly evolving diagnostic criteria for sepsis, studies that use other reference standards or predate the Sepsis-1 definition may also be considered for inclusion. This decision will be determined based on the definition reported by the study authors, the fulfilment of the inclusion criteria outlined in this protocol, and the agreement between the two reviewers during full-text screening.

Exposure

Studies evaluating the concentration of PC in the blood of adult patients with sepsis within 24 hours of study enrolment will be included. Included studies must also evaluate at least one of the following:

1. PC's use as an independent diagnostic indicator for sepsis,
2. PC's use as an independent prognostic indicator for mortality in patients with sepsis.

The control patients for the diagnostic outcome are patients with non-sepsis whose PC levels were measured within 24 hours of study enrolment. The control patients for our prognostic outcome are surviving patients whose PC levels were measured within 24 hours of study enrolment. Studies for which there are insufficient data to obtain or calculate either mean PC levels, or the sensitivity, specificity, and area under the receiver operating curve (AU-ROC) of PC as a biomarker, will be excluded.

Outcomes

Primary outcomes

1. The diagnostic accuracy of PC in adult patients with sepsis.
2. The prognostic accuracy of PC for mortality in adult patients with sepsis.

Secondary outcome

1. The diagnostic accuracy of PC for the diagnosis of sepsis with or without DIC in adult patients.

Information sources

Search strategy

The search will be conducted using PubMed, EMBASE, CINAHL, Medline and CENTRAL databases, and aims to find published articles only. Databases will be searched from inception through 20 January 2021, and study selection will be limited to studies written in English. A search strategy was developed on PubMed using keywords, Medical Subject Headings, and Boolean logic operators (online supplemental appendix 1). The citations from all included studies will be manually searched for additional articles for inclusion. In addition, any papers meeting inclusion criteria identified during the research process and in consultation with experts in sepsis biomarker research will be included as well. The PubMed search strategy will be adapted for searches in the remaining databases.

Study records

Selection process

Results of the literature search will be imported into Covidence and duplicates will be removed.²³ Study selection will occur in a two-step process and will be recorded in a PRISMA flow diagram. First, the title and abstracts of records will be screened in duplicate by two authors (VC and KP) against the eligibility criteria. Next, potentially eligible studies will undergo a full-text assessment by two authors (VC and KP) for inclusion in the study. The reasons for study exclusion following full-text review as well as the excluded articles will be recorded. Disagreements regarding the eligibility of studies will be resolved by discussion or consultation with a third reviewer (FS). To avoid duplicate publication bias, only the earliest version of papers that use the same patient data will be included. If the earliest paper is missing required outcome data, the data will be obtained from the duplicate publications where possible.

Data extraction and management

For studies that meet the eligibility criteria, information on patient and outcome characteristics will be extracted by two authors (VC and KP). A standardised data extraction form will be made in Excel and will be piloted on a randomly selected subset of the included papers. Any disagreements between reviewers during extraction will be resolved by discussion or consultation with a third reviewer (FS). The following information will be extracted from published articles and the corresponding supplemental material:

1. Bibliographic details: first author, publication year, study setting, type of study (prognostic or diagnostic) and country.
2. Demographic and clinical information: study size, mean age, sepsis definition used, patient population description (severity of sepsis), mortality proportion and follow-up duration for mortality.
3. PC measurement: time point of measurement, and PC assay used.
4. Study outcomes: mean biomarker levels, PC threshold values, AU-ROC, sensitivity, specificity, positive and negative predictive values.

Assessment of risk of bias

To assess the risk of bias (RoB) in each included study, two reviewers (VC and KP) will assess each study independently. Any disagreements will be resolved by discussion or a third reviewer (FS). Agreement between the two reviewers will be reported using percentage agreement and a weighted kappa statistic (κ).

Studies included for evaluation of PC's prognostic accuracy will be assessed independently in duplicate using the Quality in Prognostic Studies (QUIPS) tool.²³ The QUIPS tool uses six factors to assess bias in prognostic studies: study participation, study attrition, prognostic factor measurement, confounding measurement and account, outcome measurement, and analysis and reporting. A decision will be made as to whether each factor is high, moderate or low RoB. Studies included for evaluation of PC's diagnostic accuracy will be assessed independently in duplicate using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool.²⁴ The QUADAS-2 tool evaluates RoB in four domains: patient selection, index test, reference standard and flow/timing. A decision will be made as to whether each factor is high or low RoB. If the study provides insufficient information to make a decision for specific categories and information cannot be obtained from the primary study author, the RoB will be classified as unclear.

Studies that report on both PC's use as a diagnostic and prognostic biomarker will be evaluated using both tools. A RoB graph and summary figure will be created in Review Manager V.5.4.1 (RevMan) for prognostic and diagnostic studies independently.

Dealing with missing data

If there are insufficient data to conduct data extraction or RoB assessment, the primary author will be contacted by email to request additional information. The impact of any missing data on the results will be discussed in the final publication.

Data analysis

Statistical analysis

Data will be synthesised for meta-analysis using RevMan V.5.4.1, if there are data from at least two studies available. To assess the diagnostic accuracy of PC, mean biomarker levels in individuals with and without sepsis will be extracted, along with their respective SD. To assess the prognostic strength of PC, mean biomarker levels in survivors and non-survivors will be extracted along with their respective SD. This data will be used to create forest plots of the standardised mean difference (SMD) of PC biomarker levels and will be reported as SMD \pm the 95% CI in each of the patient populations. We will also extract the sensitivity and specificity and their respective 95% CIs for each of our outcomes. This data will be used to create forest plots of the pooled sensitivity and specificity. In addition, two hierarchical summary receiver operator characteristic curves (HSROC), one for prognostic and another for diagnostic studies, will be generated to assess biomarker test accuracy. This method was chosen as it accounts for both within and between study variability.²⁵

Reporting of prognostic and diagnostic test accuracy varies widely. In some studies, sensitivity and specificity may not be reported and insufficient data may be available to obtain a 2x2 contingency table necessary for HSROC construction and sensitivity and specificity analysis. If this data cannot be obtained for a significant portion of the studies (>50% of studies), sensitivity, specificity, and AU-ROC values of each independent study will be summarised in a table.

Testing for heterogeneity

Heterogeneity will be identified by visual inspection of forest plots and HSROC curves. The statistical heterogeneity of study results will be analysed using the I^2 statistic, which assesses the percentage of variability due to heterogeneity rather than chance in effect estimates. If I^2 is greater than 50%, this will constitute significant heterogeneity and a random-effects model will be used when creating the forest plot meta-analysis. If I^2 is greater than 50%, sensitivity analyses will be conducted to identify the effect a study's RoB has on heterogeneity.

Sensitivity and subgroup analysis

Sensitivity analysis will be performed to determine the influence of RoB on the outcomes being investigated. Studies will be grouped by their RoB designation for SMD forest plot and HSROC analysis to determine if this affects study findings. This will help to assess the strength of the study conclusions and the impact that methodological quality has on study results. To investigate additional

sources of heterogeneity, subgroup analysis will be explored for the following factors if sufficient studies are available.

1. For all outcomes: sepsis definition (Sepsis-1, Sepsis-2, Sepsis-3).
2. For primary prognostic outcome: type of mortality follow-up (eg, 28-day mortality, in-hospital mortality etc.).

Meta-biases

If a sufficient number of studies are identified for both our diagnostic and prognostic studies (>10 studies), we will investigate small studies bias using Deek's funnel plot. This test was selected because it was developed specifically for the assessment of publication biases in literature reviews.²⁶

Confidence of cumulative evidence

The certainty of evidence for pooled outcomes will be assessed according to Grading of Recommendations, Assessment, Development and Evaluation methodology.²⁷ Assessments will be made in duplicate (VC and KP) with conflicts resolved through discussion or a third reviewer (FS).

Discussion

Over the past two decades, the clinical definition of sepsis has evolved, with the current Sepsis-3 definition guiding clinical care. The *Surviving Sepsis* campaign emphasises the use of biomarkers to support the clinical assessment of patients.⁸ However, in the Sepsis-3 definition, the role of biomarkers remains undefined, highlighting the need to better understand how biomarkers can strengthen an evolving clinical definition.¹ To date, only lactate, procalcitonin and C reactive protein have been commonly used in clinical practice for adult sepsis. However, these biomarkers are limited in their sensitivity and specificity.²⁸⁻³⁰ Given PC's role in multiple inflammation and coagulation pathways, its rapid consumption during sepsis, and decreased transcription in patients with sepsis, it is a worthwhile candidate for evaluation as a sepsis biomarker. Therefore, clinicians caring for patients with sepsis require a comprehensive evaluation of PC's value as a biomarker to inform evidence-based practices.

Using a rigorous systematic review and meta-analysis methodology, this paper will be the first meta-analysis summarising the evidence of PC's diagnostic accuracy and prognostic strength as a biomarker for adult sepsis. From a diagnostic perspective, PC could allow for the early detection of sepsis, enabling early therapeutic intervention and the reduction of DIC, organ failure and death. From a prognostic perspective, identifying patients at high risk for mortality within the early stages of sepsis can help tailor treatment intervention and hospital admission decisions.³¹ The strengths of this review include its extensive search of five databases and comprehensive RoB assessments using QUADAS-2 and QUIPS tools. Potential limitations include missed data from unpublished

articles and preliminary results of ongoing studies. In addition, there may be challenges with the meta-analysis due to the heterogeneity in the primary studies. This will be addressed by conducting a sensitivity analysis to determine the effect of RoB on heterogeneity. Overall, it is anticipated that the results of this project will address an important knowledge gap by summarising the existing evidence on PC's utility as a sepsis biomarker. This can be used to inform the direction of future research and clinical practice related to the use of biomarkers for sepsis.

Ethics and dissemination

Given this is a systematic review and meta-analysis, there is no requirement for ethics approval. Findings will be disseminated through peer-reviewed publication.

Twitter Alison Fox-Robichaud @drfoxrob

Contributors This protocol was written by VC (BSc candidate), FS (MSc candidate) and KP (BSc candidate) contributed by editing the protocol. AF-R provided general supervision, in addition to assisting with technical editing, language editing and proofreading. All authors approved the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID ID

Alison Fox-Robichaud <http://orcid.org/0000-0001-9912-3606>

REFERENCES

- Singer M, Deutschman CS, Seymour CW, *et al.* The third International consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016;315:801.
- Leligdowicz A, Matthay MA. Heterogeneity in sepsis: new biological evidence with clinical applications. *Crit Care* 2019;23:80.
- Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med Overseas Ed* 2013;369:840–51.
- Schouten M, Wiersinga WJ, Levi M, *et al.* Inflammation, endothelium, and coagulation in sepsis. *J Leukoc Biol* 2008;83:536–45.
- Grover SP, Mackman N, Grover Steven P, Nigel M. Tissue factor. *Arterioscler Thromb Vasc Biol* 2018 ;;38:709–25. Apr 1.
- Toitl LJ, Swystun LL, Pepler L, *et al.* Protective effects of activated protein C in sepsis. *Thromb Haemost* 2008;100:582–92.
- Rudd KE, Johnson SC, Agesa KM, *et al.* Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the global burden of disease study. *The Lancet* 2020;395:200–11.
- Rhodes A, Evans LE, Alhazzani W, *et al.* Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med* 2017;43:304–77.
- Gaini S, Relster MM, Pedersen C, *et al.* Prediction of 28-days mortality with sequential organ failure assessment (SOFA), quick SOFA (qSOFA) and systemic inflammatory response syndrome (SIRS) - a retrospective study of medical patients with acute infectious disease. *Int J Infect Dis* 2019;78:1–7.
- April MD, Aguirre J, Tannenbaum LI, *et al.* Sepsis clinical criteria in emergency department patients admitted to an intensive care unit: an external validation study of quick sequential organ failure assessment. *J Emerg Med* 2017;52:622–31.
- Williams JM, Greenslade JH, McKenzie JV, *et al.* Systemic inflammatory response syndrome, quick sequential organ function assessment, and organ dysfunction: insights from a prospective database of ED patients with infection. *Chest* 2017;151:586–96.
- Pierrakos C, Velissaris D, Bisdorff M, *et al.* Biomarkers of sepsis: time for a reappraisal. *Crit Care* 2020;24:287 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7273821/>
- Shorr AF, Bernard GR, Dhainaut J-F, *et al.* Protein C concentrations in severe sepsis: an early directional change in plasma levels predicts outcome. *Crit Care* 2006;10:R92.
- Dahlbäck B, Villoutreix BO. The anticoagulant protein C pathway. *FEBS Lett* 2005;579:3310–6.
- Derhaschnig U, Reiter R, Knöbl P, *et al.* Recombinant human activated protein C (rhAPC; drotrecogin alfa [activated]) has minimal effect on markers of coagulation, fibrinolysis, and inflammation in acute human endotoxemia. *Blood* 2003;102:2093–8.
- Vary TC, Kimball SR. Regulation of hepatic protein synthesis in chronic inflammation and sepsis. *Am J Physiol* 1992;262:C445–52.
- Liaw PCY. Endogenous protein C activation in patients with severe sepsis. *Crit Care Med* 2004;32:S214–8.
- Shamseer L, Moher D, Clarke M, *et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349:g7647.
- Seymour CW, Liu VX, Iwashyna TJ, *et al.* Assessment of clinical criteria for sepsis: for the third International consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016;315:762.
- Bone RC, Balk RA, Cerra FB, *et al.* Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. the ACCP/SCCM consensus conference committee. American College of chest Physicians/Society of critical care medicine. *Chest* 1992;101:1644–55.
- Levy MM, Fink MP, Marshall JC, *et al.* 2001 SCCM/ESICM/ACCP/ATLS/SIS international sepsis definitions conference. *Intensive Care Med* 2003;29:530–8.
- Harrison H, Griffin SJ, Kuhn I, *et al.* Software tools to support title and Abstract screening for systematic reviews in healthcare: an evaluation. *BMC Med Res Methodol* 2020;20:7.
- Hayden JA, van der Windt DA, Cartwright JL, *et al.* Assessing bias in studies of prognostic factors. *Ann Intern Med* 2013;158:280–6.
- Whiting PF, Rutjes AWS, Westwood ME, *et al.* QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;155:529–36.
- Lee J, Kim KW, Choi SH, *et al.* Systematic review and meta-analysis of studies evaluating diagnostic test accuracy: a practical review for clinical researchers-part II. statistical methods of meta-analysis. *Korean J Radiol* 2015;16:1188–96.
- Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. *J Clin Epidemiol* 2005;58:882–93.
- Oxman A, Guyatt G, Guyatt G. *Grade Handbook for grading quality of evidence and strength of recommendations.* The GRADE Working Group, 2013.
- Wu C-C, Lan H-M, Han S-T, *et al.* Comparison of diagnostic accuracy in sepsis between presepsin, procalcitonin, and C-reactive protein: a systematic review and meta-analysis. *Ann Intensive Care* 2017;7:91 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5585118/>
- Liu Z, Meng Z, Li Y, *et al.* Prognostic accuracy of the serum lactate level, the SOFA score and the qSOFA score for mortality among adults with sepsis. *Scand J Trauma Resusc Emerg Med* 2019;27:51.
- Nguyen HB, Rivers EP, Knoblich BP, *et al.* Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. *Crit Care Med* 2004;32:1637–42.
- Biron BM, Ayala A, Lomas-Neira JL. Biomarkers for sepsis: what is and what might be? *Biomark Insights* 2015;10:BMI.S29519–17.