Optimizing the diagnosis of serious infections in adults in general practice using biomarkers.

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Abstract

Objectives

This systematic review aims to summarize existing literature identifying promising biomarkers to assist in rapid and accurate diagnosis of serious infections such as sepsis, pneumonia, pyelonephritis and acute exacerbation of COPD.

Materials and methods

We searched PubMed, EMBASE, HTA, CINAHL, Web of Science Core Collection and Cochrane in April 2023 for prospective studies concerning adults with a suspected infection in ambulatory care, of whom a blood sample was drawn within 12 hours after presentation.

Results

Out of 9628 articles, 98 studies were included: 21 concerning pneumonia and 77 concerning sepsis. For pneumonia, we found an AUC of 0.80 for CRP and 0.73 for PCT. For sepsis, we found an AUC of 0.74 for PCT, 0.72 for presepsin, 0.68 for IL-6, 0.66 for CRP and 0.59 for lactate.

Conclusion

We found a few promising biomarkers: CRP at a cut-off of 30 mg/L or lower to rule out pneumonia and presepsin or CRP combined with clinical findings to rule out sepsis. However, more research is needed on this.

Samenvatting

Doelstellingen

Deze systematische review heeft als doel om in de bestaande literatuur veelbelovende biomarkers te identificeren, die nuttig zijn voor de snelle en accurate diagnose van ernstige infecties zoals sepsis, pneumonie, pyelonefritis en een acute COPD exacerbatie.

Materialen en methoden

We hebben op PubMed, EMBASE, HTA, CINAHL, Web of Science Core Collection en Cochrane gezocht in april 2023 naar prospectieve studies over volwassenen met een vermoeden van infectie in de eerste lijn, bij wie een bloedonderzoek gebeurde binnen de 12 uur na presentatie.

Resultaten

Uit 9628 publicaties zijn er 98 geïncludeerd: 21 studies over pneumonie en 77 over sepsis. De AUC (zone onder de curve) voor pneumonie bedroeg 0.80 voor CRP en 0.73 voor PCT. De AUC voor sepsis bedroeg 0.74 voor PCT, 0.72 voor presepsine, 0.68 voor IL-6, 0.66 voor CRP en 0.59 voor lactaat.

Conclusie

We vonden enkele veelbelovende biomarkers: CRP aan een cut-off van 30 mg/l of lager is veelbelovend voor het uitsluiten van pneumonie en presepsine of CRP in combinatie met klinische factoren zijn veelbelovend voor het uitsluiten van sepsis. Hierover is echter nog meer onderzoek nodig.

Introduction

Serious infections in adults include a variety of conditions that can lead to significant morbidity and mortality. They pose serious diagnostic challenges due to their rapid progression and wide range of nonspecific symptoms that overlap with other conditions. For example symptoms like fever, cough, or dyspnoea may indicate a respiratory infection, but they can also be caused by non-infectious conditions like heart failure, pulmonary embolism, or asthma. Early and precise diagnosis is crucial, as it reduces the time to treatment, leading to better patient outcomes.(1) Delaying treatment of a serious infection by 8-24 hours may result in mortality rates that are 8 to 22 times higher than when treatment is initiated immediately.(2,3)

The most common serious infections include sepsis, pneumonia, pyelonephritis and acute exacerbation of chronic obstructive pulmonary disease (AECOPD).(3–8)

Sepsis is a life-threatening condition resulting from the body's dysregulated response to an infection, which injures its own tissue and organs and leads to organ dysfunction.(1,4) It is estimated that 51 to 300 per 100.000 people are annually affected by severe sepsis.(4) According to the Global Burden of Disease Study sepsis affected 48.9 million people worldwide in 2017, of which 11 million patients died that year, which makes it one of the leading causes of deaths worldwide.(9) Symptoms of sepsis can be numerous since the infection site can be anywhere in the body and they can vary in severity and change rapidly, making it even harder to diagnose. Over the years, different definitions of sepsis and septic shock have been used. The initial definition (consensus conference in 1991 and an expansion in 2001 (sepsis-2)) included the combination of systemic inflammatory response syndrome (SIRS) criteria and a suspected infection. The SIRS criteria, of which 2 or more were needed, were: body temperature >38°C or <36°C, heart rate >90/min, respiratory rate >20/min or PaCO2 <32 mm Hg (4.3 kPa), and white blood cell count (WBC) >12 000/mm3 or <4000/mm3 or >10% immature bands.(7) The most recent definition of sepsis is based on the sepsis-3 criteria: sepsis is defined as a suspected or documented infection in combination with organ dysfunction, identified by the Sequential Organ Failure Assessment (SOFA) score. Organ dysfunction is described as an acute change of 2 or more SOFA points in response to an infection. To calculate the SOFA score, six different organ systems are assessed: the respiratory system (arterial blood oxygenation), the cardiovascular system (mean arterial pressure (MAP)), the hepatic system (bilirubin), coagulation (platelet count), the renal system (creatinine or urine output), and the neurological system (Glasgow Coma Scale).(7) A blood test and an arterial blood gas are necessary to calculate the score, which is time-consuming and not readily available in all health settings.

Pneumonia is an acute inflammation of the lower respiratory tract. Pneumonia affects about 2 to 13 adults per 1000 people each year.(5) It was the leading cause of death from infectious diseases worldwide in 2015 and the fifth most common cause of death overall, responsible for 2.74 million deaths that year.(6) It usually presents with fever, cough, shortness of breath and malaise.(10) However 20% of pneumonia patients present with gastro-intestinal symptoms and elderly patients may present with confusion as the only symptom.(11,12) Physical examination (auscultation, saturation) is widely used, but is neither sensitive nor specific for pneumonia (56 and 67% respectively).(12) To obtain the diagnosis of pneumonia, a chest radiography is often used but this is time-consuming and may be false negative in the early stages of disease.(11)

In the United States it is estimated that pyelonephritis affects 15 to 17 per 10.000 women and 3 to 4 per 10.000 men every year.(13) Pyelonephritis is an infection of the upper urinary tract, characterized by dysuria, fever, flank pain, nausea and vomiting.(14) However, in older adults, for example, fever is absent in 30% and symptoms are limited to gastro-intestinal or pulmonary complaints in 20%.(15) Prognosis of pyelonephritis is good when treated timely, but if not, it can lead to serious complications such as septic shock and renal failure.(14) To confirm diagnosis, a urinalysis and culture need to be performed, but these are time-consuming. Dipsticks are easily available and already routinely used in the ambulatory care setting; their sensitivity and specificity in ambulatory care setting are reasonable: 74-94% and 94-98% for leukocyte esterase test, and 35-85% and 92-100% for nitrite test respectively.(14) Unfortunately dipsticks don't differentiate between a lower urinary tract infection or pyelonephritis.

Chronic obstructive pulmonary disease (COPD) was the third leading cause of death globally in 2019, responsible for 3.23 million deaths.(16) It is a common disease: in 2013 over 300 million people had a COPD diagnosis according to the Global Burden of Disease Study.(17) Of these patients, an average of 22-40% has a moderate to severe exacerbation annually.(18) An acute exacerbation of COPD is an acute worsening of respiratory symptoms accompanied by physiological deterioration, which is caused by increased inflammation of the airway. This inflammation can be infectious or non-infectious, and their diagnosis and treatment differ.(8) Infectious exacerbations, triggered by bacterial or viral infections, are diagnosed through symptoms (increased mucus production, fever) and elevated white blood cell count, or with further testing such as sputum cultures or chest X-rays. Treatment often involves antibiotics alongside bronchodilators and corticosteroids. Non-infectious exacerbations, caused by air pollution or allergens, show similar symptoms but often lack fever or infection markers. Diagnosis relies on ruling out infection and treatment focuses on bronchodilators and steroids.(19) Patients with a exacerbation needing hospitalization are shown to have more risk of being re-hospitalised within 8 weeks for another exacerbation.(8) Early recognition of an exacerbation results in earlier treatment, leading to shorter exacerbation-periods and lower hospitalization rates.(19)

There is a need to quickly and objectively identify or rule out serious infections. Biomarkers may prove useful as a low-invasive and fast way to diagnose them. A biomarker is defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".(20) An ideal biomarker should be an easy and inexpensive test that is not only sensitive and specific to the diagnosis of the infection, but it can also be used to quantify the severity of infection in the absence of symptoms and to monitor the response to treatment.(21) Several biomarkers, such as procalcitonin, C-reactive protein, interleukin-6, lactate and white blood cell count, are suggested for the diagnosis of infections.

Procalcitonin (PCT) is a prohormone of calcitonin. In healthy individuals, PCT is present below a detectable level in the blood. During inflammation, PCT production is stimulated by inflammatory cytokines like IL-1β, TNF-α, and bacterial endotoxins.(22) Upon bacterial infection, PCT levels significantly increase within 2-3 hours, peaking at 6 hours.(23) The initial rise in PCT levels is typically less pronounced in viral infections compared to bacterial infections, making PCT a possible marker for distinguishing between the two.(24) Elevated PCT levels are linked to diagnosing pneumonia and bacterial sepsis, but it can also be elevated in non-infectious

conditions like cirrhosis and burns.(25). Elevated PCT levels suggest bacterial infection as a cause of COPD exacerbation, aiding in the decision to use antibiotics.(18)

C-reactive protein (CRP) is a protein synthesized by the liver in response to inflammatory cytokines, particularly IL-6.(24) Its production is upregulated in response to infection or inflammation, starting within 4-6 hours and peaking at 36-50 hours.(23) Elevated CRP levels are associated with the severity of pneumonia and organ failure, as well as the severity of sepsis, although CRP is not specific to infections and can be elevated due to other conditions like trauma, surgery, burns, and autoimmune diseases.(23)(26) CRP can also help differentiate between stable COPD and exacerbations, providing a measure of the inflammatory burden.(18)

Interleukin-6 (IL-6) is a pro-inflammatory cytokine produced in response to infections and tissue damage. It plays a central role in the acute-phase response, stimulating the production of CRP and other acute-phase proteins by the liver.(27) IL-6 levels rise rapidly in response to infections as opposed to the slower rising CRP production. Elevated IL-6 levels are associated with higher mortality risk and correlate well with clinical severity scores such as the pneumonia severity index (PSI) and the CURB-65.(23) IL-6 is an early marker for pneumonia and sepsis, although it is elevated in a range of inflammatory conditions.(23)(26,28)

Lactate is a metabolic byproduct produced under anaerobic conditions and is commonly elevated in sepsis due to tissue hypoxia and impaired cellular metabolism. High lactate levels indicate poor tissue perfusion and oxygenation, which are critical components of sepsis pathophysiology.(29) Elevated lactate levels are associated with increased mortality in sepsis and septic shock, making it a key biomarker for assessing the severity of sepsis and guiding resuscitation efforts.(26,28)

White blood cell (WBC) count and its differentiation, such as the eosinophil levels and neutrophil to lymphocyte ratio, are commonly used to assist in diagnosing infections. Eosinophils are involved in allergic responses, parasitic infections and play a role in airway inflammation. Their levels can help identify a subset of COPD exacerbations characterized by eosinophilic inflammation. Neutrophil-to-Lymphocyte Ratio (NLR) reflects systemic inflammation. An elevated NLR is associated with worse outcomes in COPD exacerbations, indicating a higher inflammatory state and potential for more severe exacerbations.(18,30)

Numerous biomarkers have already been identified in literature, with at least 178 different biomarkers described for sepsis alone.(31) The ideal biomarkers have yet to be discovered, as most biomarkers either lack sufficient sensitivity and specificity or have not been examined in large-scale studies.(32,33) The development and implementation of highly sensitive and specific biomarkers are critically needed, particularly in ambulatory care settings, such as during initial presentations in emergency departments or general practitioners' offices. In these contexts, the availability of reliable biomarkers with high sensitivity and specificity is essential to facilitate prompt initiation of the right treatment, ultimately improving patient outcomes and reducing the diagnostic uncertainty. That is why this systematic review aims to summarise existing literature identifying promising biomarkers to assist in rapid and accurate diagnosis of serious infections such as sepsis, pneumonia, pyelonephritis and acute exacerbation of COPD.

Methods

We conducted a diagnostic accuracy systematic review. The objective of this study was to evaluate the diagnostic accuracy of blood biomarkers for the most often occurring serious infections in adults visiting ambulatory care.(34–36)

Study participants had to be adults, defined as being 18 years or older, suspected of having an infection and presenting in an ambulatory care setting. A blood sample had to be drawn and analysed either by point of care testing or in a central laboratory within 12 hours after presentation. In search of serious infections, we included the conditions pneumonia, sepsis and bacteraemia, pyelonephritis/pyelitis and acute infectious exacerbation of chronic obstructive pulmonary disease (AECOPD).
Optimal reference standards were disease-specific: an infiltrate on chest radiograph or computer tomography (CT) within 72 hours after hospital admission for pneumonia; acute worsening of symptoms such as dyspnoea, cough and/or sputum production in a patient with a spirometry confirmed COPD (FEV1/FVC < 0.70) resulting in hospital admission or visit to the emergency room for AECOPD; suspected or blood culture proven infection (bacteraemia) and an acute increase of ≥2 SOFA points (organ dysfunction) for sepsis; positive imaging on dimercaptosuccinic acid (DMSA) renal scan or single pathogen of 10^5 colony forming units/ml in urine culture, with symptoms and signs attributable to a complicated UTI for pyelonephritis/pyelitis. When alternative reference standards were used, we judged the validity of these reference standards or consulted a clinician expert.

We searched PubMed, EMBASE, HTA, CINAHL, Web of Science Core Collection and Cochrane in April 2023. In addition, we checked the reference lists of included studies. We searched all databases using MESH terms that matched our review question according to the Patient – Index test – Reference standard – Target condition – Setting (PIRTS) (Table 1). P = adults; I = blood biomarkers; R = infection-specific e.g. x-ray, blood culture, … ; T = most often occurring serious infections in adults visiting ambulatory care (pneumonia, sepsis/bacteraemia, acute infectious exacerbation of chronic obstructive pulmonary disease (AECOPD), and pyelonephritis); S = ambulatory care. The search string was developed in cooperation with a biomedical reference librarian of the KU Leuven Libraries.

We included diagnostic accuracy studies (cross-sectional prospective and retrospective cohort studies) and single-gate nested case-control studies (in which cases and controls are sampled from the same source population). Case-control studies were excluded, given their high potential for bias.(37) Studies were excluded when the total sample size was smaller than 50, because these studies would include only a few subjects with the target condition and would be prone to selection bias. Case-report studies were excluded for this reason as well. Additionally, all types of reviews, conference abstracts, letters, editorials, study protocols, comments and prognostic studies without any diagnostic information were excluded. We only present data from prospective studies for the analyses, because retrospective studies tend to have more bias, resulting in an overestimation of accuracy of outcomes.(38)

Language restrictions were imposed only when no reliable translation was available. Inclusion of languages other than English, French, German, Dutch and Spanish were therefore subject to the availability of a reliable translation.

Abstract and full text screening was conducted pairwise by four independent researchers using Covidence (AJ, JG, SG, AV).(39) When evaluations did not match, a third reviewer (TS) assessed the eligibility of this study.

Two independent reviewers (AJ, JG, SG, AV) assessed risk of bias in pairs using all QUADAS-2 items and a third reviewer (TS) assessed all disagreements, using Microsoft Excel and RevMan.(40) Studies were not excluded from the review based on the risk of bias assessment, but the results of the assessment were used in the interpretation of the results. In addition, specific aspects, i.e. non-consecutive inclusion and retrospective data collection, were used in sensitivity analyses.

Data for diagnostic accuracy was collected using Microsoft Excel and summarized in 2x2 tables using RevMan. Statistical analyses were made using RevMan, including Forest plots and AUC curves. The diagnostic accuracy was expressed as sensitivity and specificity, predictive values, likelihood ratios and/or Area Under the Receiver Operating Characteristic curve (AUROC), including their 95% confidence intervals.

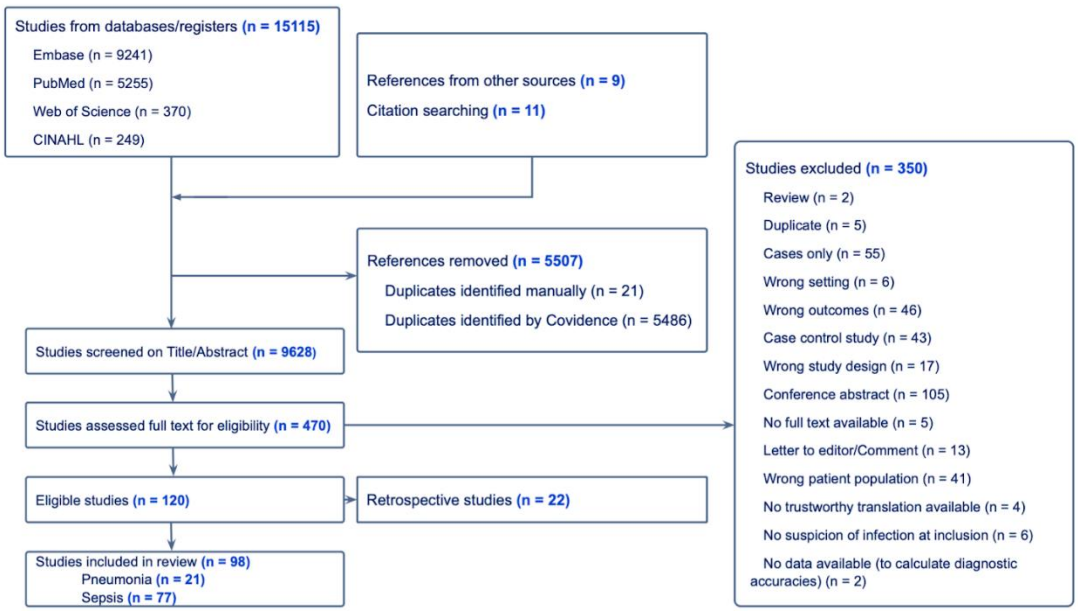
The presence of clinical heterogeneity and heterogeneity in accuracy and/or threshold effect was assessed and described. Data was pooled when at least 4 studies (with limited clinical heterogeneity) were available for a particular outcome, using a bivariate model for binary data. When multiple thresholds where reported for continuous biomarkers, a Hierarchical Summary Receiver Operating Characteristic (HSROC) meta-analysis was conducted using the Steinhauser method, taking into account the inherent correlation of data originating from the same study population (Diagmeta package, R statistical software version 4.3.3).

Subgroup analyses by age groups (all adults vs. 65+ years), by setting (primary vs. emergency care) and by risk of bias regarding participant selection, conduct or interpretation of the index tests and the reference standard (as assessed using the QUADAS-2 tool) were made when possible.

Results

Upon our search in April 2023, we retrieved 15,115 studies that matched our review question: 9241 on Embase, 5255 on PubMed, 370 on Web Of Science and 249 on CINAHL. Based on citation and reference searching, we included another 20 studies. When loading these studies into Covidence, 5486 studies were identified as duplicates and were removed. Another 21 duplicates were removed manually. This left us with 9628 studies to screen based on title and abstract, of which 9158 did not match our review question. The remaining 470 studies were screened on full text. Three-hundred and fifty studies were excluded, with the most frequent reasons for exclusion being conference abstracts (n = 105), cases only (n = 55), wrong outcomes (n = 46), case-control study (n = 43), wrong patient population (n = 41) and wrong study design (n = 17). Other reasons for exclusion were a letter to editor/comment (n = 13), no suspicion of infection at inclusion (n = 6), wrong setting (n = 6), duplicate (n = 5), no full text available (n = 5), no trustworthy translation available (n = 4), review (n = 2) or no data available to calculate diagnostic accuracies (n = 2). This resulted in 120 studies that matched our review question, as shown in the PRISMA flowchart (Figure 1). Of these, 22 were retrospective. Therefore we identified 98 prospective studies: 21 studies on pneumonia and 77 studies on sepsis. We will discuss the results per condition.

Figure 1: PRISMA flowchart



PNEUMONIA

Quality appraisal (Quadas-2)

We identified 21 studies concerning pneumonia.(41–61) Their risk of bias summaries are presented in Figure 2.

Patient selection was a common reason for scoring high risk of bias. Six studies did not avoid inappropriate exclusions.(45,47,52,53,59,60) One study used only pregnancy as a reason for exclusion, as it influences the range of normal infection markers.(60) In another study, people with preexisting COPD were excluded.(47) Patients who did not need hospitalization were excluded in a third study.(45) People who received antibiotics or who got a diagnosis of pneumonia at a later stage were excluded from all analyses in another study.(59) Both studies by Hopstaken et al. excluded patients with penicillin or macrolide hypersensitivity or in treatment with alkaloids or terfenadine because this was important for a randomized controlled trial executed in the same patient population, however these were unnecessary exclusions for our diagnostic review.(52,53) One study aimed to include patients consecutively, but failed because of the high prevalence of respiratory tract symptoms, resulting in high risk of bias.(43) Eight studies scored unclear risk of bias due to unclear reporting of patient sampling, due to exclusion of patients with severe dyspnoea without clear definition of "severe dyspnoea" and due to exclusion of patients with prior pneumonia (41,42,46,49,58,61).

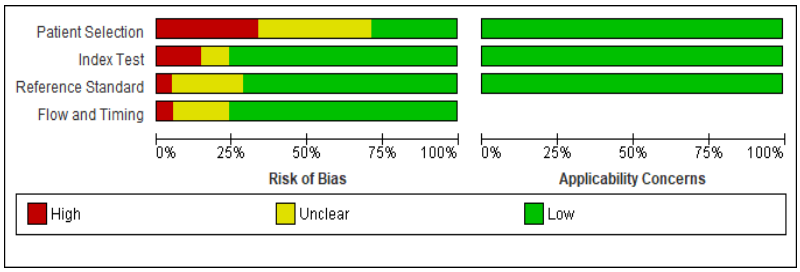
The index test was assessed at having a high risk of bias in three out of twenty-one studies. This was due to a non-prespecified threshold. Instead a calculation of the cut-off was made based on the AUC-analysis.(45,51,57) In two studies it was unclear if a threshold was prespecified.(43,59)

Regarding the reference standard, only one study was not blinded to the index test, therefore scoring a high risk of bias.(47) Five studies had an unclear risk of bias, due to unclear reporting whether the reference standard was blind to the index test.(45,46,48,49,57)

Flow and timing was scored as high risk only in one study due to the use of different reference standards among patients. Only patients with a clinical chance of pneumonia, CRP>60 or ESR>50 received a radiological evaluation.(48) No studies scored high risk of bias on time interval between index test and reference standard or inclusion of all patients in the analysis. Four studies scored unclear risk of bias concerning flow and timing due to unclear reporting about time between index test and reference test.(46,52,59,61)

There were no applicability concerns.

Figure 2: Pneumonia: Risk of bias overview



Results

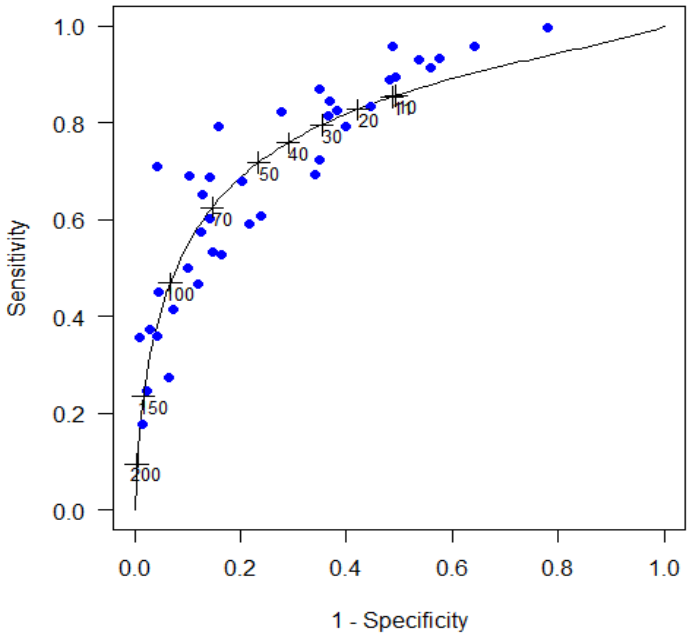
Study characteristics are shown in Table 2. Sixteen different biomarkers were assessed, of which only two were assessed in more than one study: CRP and PCT.

Fifteen studies used a chest radiograph as a reference standard.(42,43,45–49,52–59) One study used chest CT imaging.(60) Five studies used an adjudication committee that either used information on X-ray or CT findings as well as microbiological proof of infection, or based their decision on the BTS Guidelines for the Management of Community Acquired Pneumonia (CAP) in adults.(41,44,50,51,61) Eleven studies were conducted in the Emergency Department (ED).(41,45,46,48,50,51,56,57,59–61) Eight studies were implemented at the General Practitioner's (GP) Office.(42–44,52–55,58) Two studies enrolled both at the ED and in general practice.(47,49)

The total number of included patients ranged from 58 to 3104 patients. All studies included a similar age group, defined as adult patients (18 years or older).

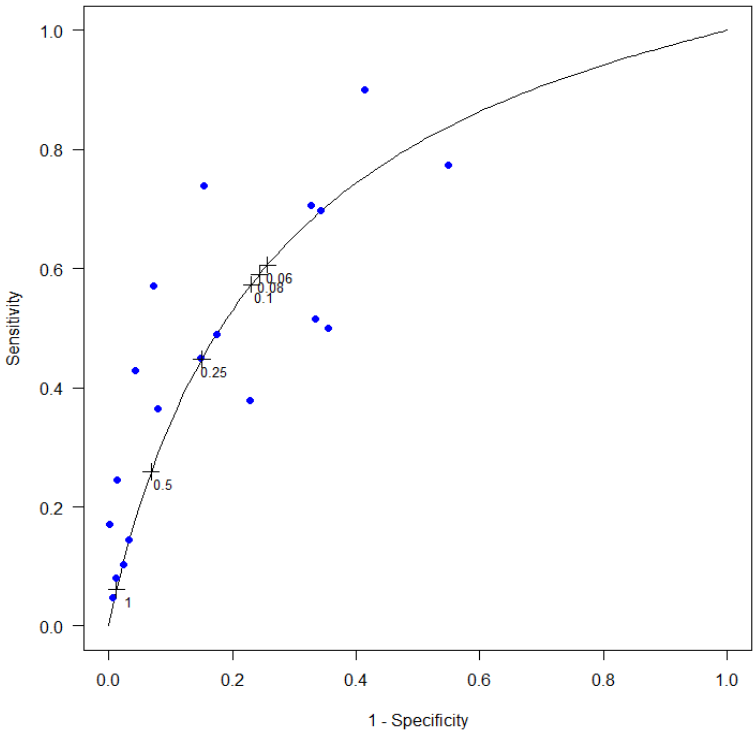
The first biomarker that was assessed is CRP at different cut-offs (Figure 3). The pooled AUC (HSROC analysis) for CRP was 0.80 (95% CI [0.72; 0.86] for sensitivity given specificity and CI [0.75; 0.84] for specificity given sensitivity) (Figure 4).

Figure 4: Pneumonia: HSROC curve for CRP. Blue dots represent individual study results, crosses indicate different cut-offs (in mg/L).



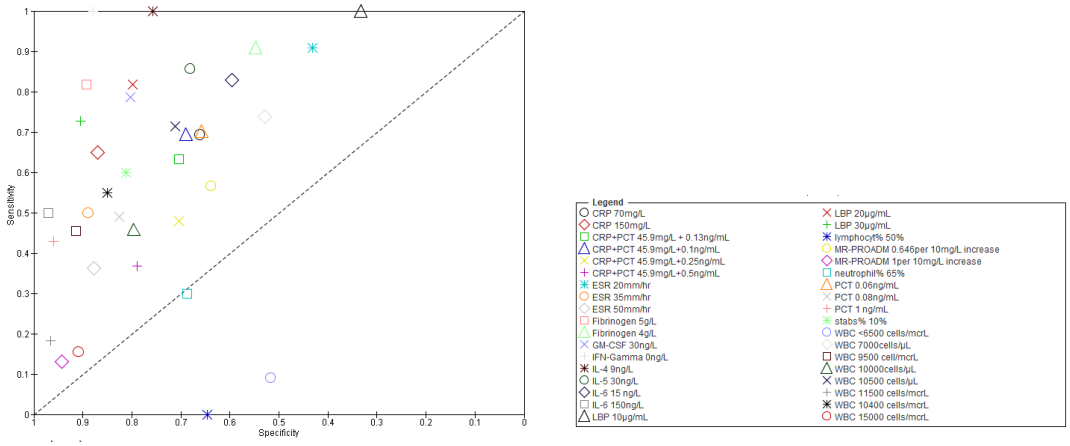
The second most often investigated biomarker was PCT at different cut-offs (Figure 5). The pooled AUC for PCT was 0.73 (95% CI [0.52; 0.85] for sensitivity given specificity and CI [0.59; 0.86] for specificity given sensitivity) (Figure 6).

Figure 6: Pneumonia: HSROC curve for PCT. Blue dots represent individual study results, crosses indicate different cut-offs (in ng/mL).



Other biomarkers investigated were only available in single studies (Figure 7). Sensitivities over 80% can be seen for ESR at 20 mm/h, fibrinogen at 4 g/L and 5 g/L, IL-4 at 9 ng/L, IL-5 at 30 ng/L, IL-6 at 15 ng/L and LBP at 10 µg/mL and 20 µg/mL (Figure 8).

Figure 8: Pneumonia: ROC plot for all biomarkers investigated in single studies.



SEPSIS

Quality appraisal (Quadas-2)

We identified 77 studies concerning sepsis.(62–138) Their risk of bias summaries are presented in Figure 9.

The most common reason for scoring high risk of bias was the index test. Twenty-nine studies were rated high risk: they all calculated the cut-off based on the outcomes of the AUC-analysis (via Youden index).(76–78,82–84,90,92,93,95,96,98,105,109–111,113–120,124,125,129,130,133) Five studies were rated unclear risk of bias: it was unclear if the cut-offs were prespecified in four studies.(65,88,94,97) And in the study by Nestor et al., some cut-offs were prespecified and some were calculated based on the outcome of the study.(102)

Sixteen studies scored high risk of bias regarding patient selection. There were inappropriate inclusion criteria in seven studies: Ahmadinejad et al.(138) included patients of 12 years old and older; Chirouze et al.(68) included patients that received antibiotics prior to the study; Karon et al.(116) included patients for whom the ED specialist ordered a sepsis panel, causing a strong preselection; Romualdo et al., Shapiro et al., Singer et al. and Tan et al.(84,87,89,93) only included patients with two SIRS criteria, also causing strong preselection. The study by Singer et al.(87) had a second reason for scoring high risk of bias: it used convenience sampling instead of random or consecutive sampling. Three other studies also used convenience sampling, and therefore scored high risk of bias.(121,123,135) The study by Jekarl et al.(117) had inappropriate inclusion and exclusion criteria: some patients had yet received antibiotics and other patients with a viral infection were excluded, additionally no informed consent was acquired. Six studies used inappropriate exclusion criteria: Gaini et al.(66) excluded patients who did not have a definitive diagnosis; Lee et al.(62) excluded residents of nursing homes, who are part of our study group, and patients with altered consciousness, a possible sign of infection; Lin et al.(110) excluded patients using anti-inflammatory medication; Lin et al.(109) used strong propensity score matching; Singla et al.(86) excluded patients with oxygen need, which can be a sign of severe infection; and Wiwatcharagoses et al.(73) excluded viral or fungal infections. Of these six studies, four also scored unclear risk of bias, since the way of sampling was not clearly mentioned.(66,73,86,110) Twenty-five studies scored unclear risk of bias: twenty-one studies also had an unclear sampling procedure(63,72,74–76,81–83,90,91,93,95,98–101,103,115,119,120,124); Paul et al.(97) used an unclear sampling procedure and unclear exclusion criteria; Yu et al.(69) used an unclear sampling procedure and we could not fully exclude a case-control design; for the study of Lucchiari et al.(105) a case-control design could not be fully ruled out; lastly, in the study of Crouser et al.(133) there was no mention of exclusion criteria.

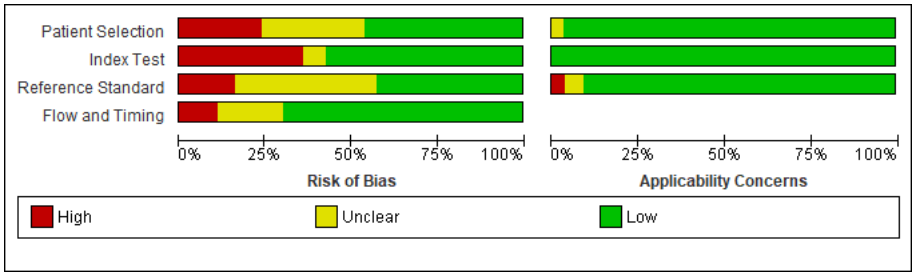
Concerning the reference standard, thirteen studies scored high risk of bias. Six studies were considered high risk of bias due to no blinding of the results of the index test, creating an incorporation bias.(90,95,96,104,105,114) Seven studies used an outdated or subjective reference standard: Ishikura et al. and Karon et al.(116,120) used the ACCP/SCCM guidelines; de Hond et al.(128) used the Modified Early Warning Score (MEWS); Jaimes et al.(119) used an expert consensus; Ahmadinejad et al., Jekarl et al. and Paul et al.(64,97,138) used a subjective clinical diagnosis made by a physician. Three of these studies also scored unclear risk of bias because it was not clear if the reference standard was blinded for the index test.(64,97,116) Thirty-one studies had an unclear risk of bias: 28 studies didn't describe if the reference standard

was executed blind to the index test(69,72,74–76,82,84,86,87,89,94,98–100,107–110,112,115,117,126,127,130–132,134,136); two studies did not mention which guidelines were used as reference standard(91,125); one study did not mention the reference standard and did not mention if it was blinded for the index test(73).

Only eight studies scored high risk of bias for flow and timing. Four studies did not include all patients (66,70,109,138) and of these studies one also had a different reference standard (138) and one was unclear about whether the same reference standard was used for all patients, resulting in unclear risk of bias; in addition it had an inappropriate time interval (71). Four studies did not use the same reference standard for all patients: Dal Ponte et al.(130) used culture, radiography or nitrite test; Olander et al.(98) performed a secondary analysis of non-admitted patient with another reference standard; Jaimes et al.(119) used an expert consensus as reference standard and had an inappropriate time interval; Ljungström et al.(107) used both sepsis-2 and sepsis-3 criteria and also scored unclear risk of bias due to unclear time interval between index test and reference standard. Fifteen other studies scored unclear risk of bias. Of the thirteen studies in which the time interval between index test and reference standard was not mentioned (69,70,72,73,84,91,105,106,111–113,125,128), two studies were also unclear in mentioning if a single reference standard was used for all patients (70,73). Two studies did not clearly mention whether all patients were included in the analysis.(74,136)

There was an applicability concern in a few studies. Four studies scored a high concern because the reference standard did not properly indicate the target condition: de Hond et al.(128) used the MEWS in combination with a probable or definite infection, indicating patients at risk of deterioration rather than diagnosing sepsis; Jaimes et al. and Gamez-Diaz et al.(119,125) used an expert consensus, which is subjective; Paul et al.(97) used blood cultures and diagnosis by a physician, which is also subjective. Two studies scored an unclear concern because of the reference standard: they did not specify which reference standard they used.(73,91) Lastly, six studies scored an unclear concern because of patient selection: Karon et al.(116) only included patients for whom the ED provider ordered a sepsis panel; Tudela et al.(81) distributed the patients in a derivation and validation group and only did all the analyses for the derivation group; Romualdo et al., Shapiro et al., Singer et al. and Tan et al.(84,87,89,93) only included patients with 2 or more SIRS criteria.

Figure 9: Sepsis: Risk of bias overview



Results

Study characteristics are shown in Table 2. Seventy-nine different biomarkers and combinations thereof were assessed, of which seven were assessed in more than one study: PCT, CRP, MDW, white blood cells, lactate, presepsin and IL-6.

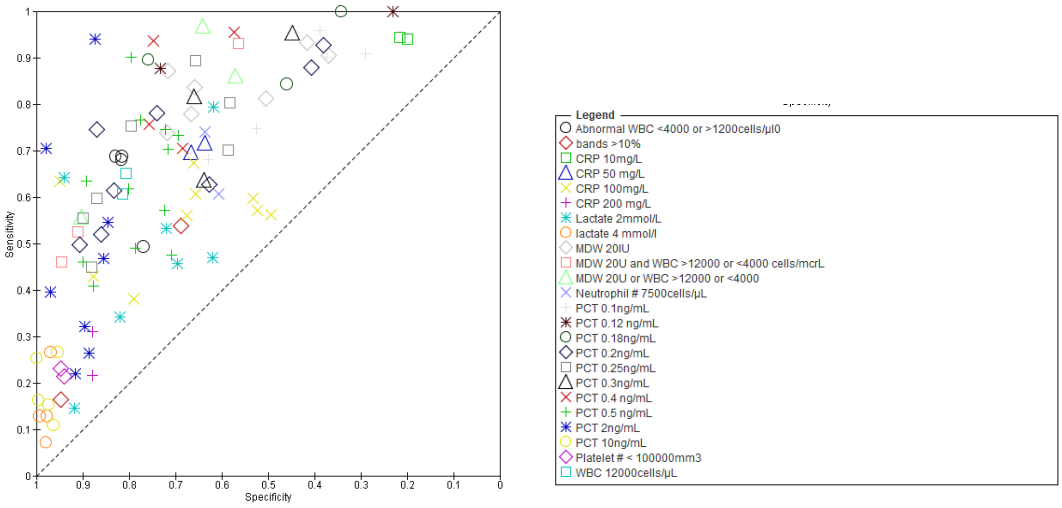
One study took place in general practice (106), all others were performed in the ED (62–105,107–138). The target disease was non-specified sepsis in thirty-eight studies, twenty-two studies focused on bacteremia, and severe sepsis; sepsis/shock; and severe sepsis/shock were investigated in respectively five, four and one studies. The remaining seven studies investigated a multiple of these target diseases.

Most studies included all adults, four set a higher age limit: more specifically ≥ 60 years(109), ≥65 years (113,135) and ≥75 years (92).

The third main difference between the selected studies is the reference standard. Sepsis-2 criteria were used in twenty studies.(64–66,73,75,77–80,82,84,95,96,109,113,121,126,130,131,133) Sepsis-3 criteria were used in eighteen studies.(69,72,74,90,92,98,100,101,104,106,111,115, 117,118,124,129,134,136) The other criteria were positive blood culture (62,63,67, 68,70,71,81,83,85,88,93,94,97,102,103,108,110,112,123,127,135,137,138), ACCP/SCCM consensus conference sepsis criteria (87,89,99,105,114,116,120), expert consensus(91,119,125) and MEWS >5 + infection(128). Five studies used sepsis-2 as well as sepsis-3 criteria.(76,86,107,122,132)

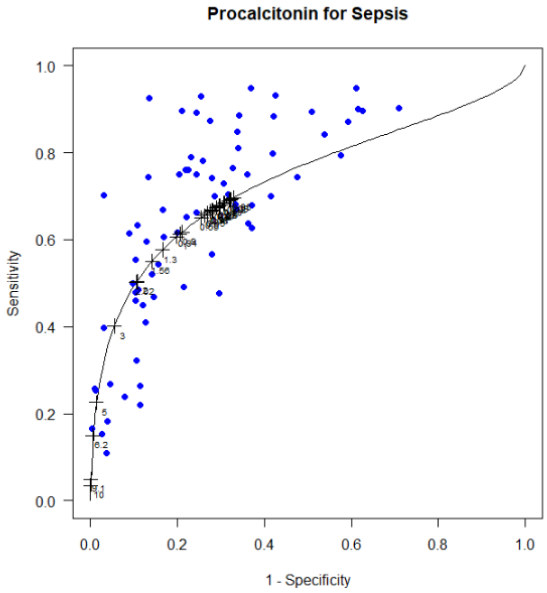
A ROC curve was created including all biomarkers that have been investigated in more than one study: bands >10%, platelets <100.000 and different cut-offs of CRP, lactate, MDW and white blood cell count and PCT (Figure 10).

Figure 10: Sepsis: ROC plot for all biomarkers investigated in more than one study.



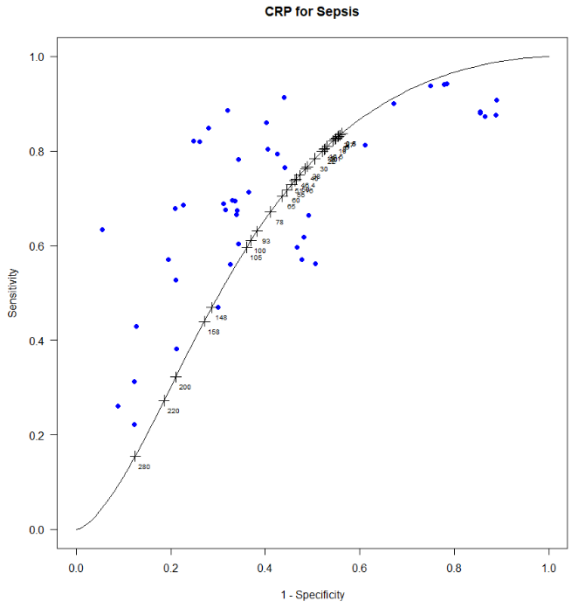
The first biomarker that was assessed is PCT at twenty-three different cut-offs, of which ten cut-offs were investigated in two or more studies (Figure 11). PCT at cut-off 0.5 ng/mL was investigated in eleven different studies.(66,75,82,83,85,100,111,135–138) The pooled AUC (HSROC analysis) for PCT was 0.74 (CI [0.65; 0.81] for sensitivity given specificity and CI [0.68; 0.80] for specificity given sensitivity) (Figure 12). The HSROC analysis included forty-three studies looking at twenty-nine different cut-offs.

Figure 12: Sepsis: HSROC curve for PCT. Blue dots represent individual study results, crosses indicate different cut-offs (in ng/mL).



The second biomarker that was assessed is CRP at 29 different cut-offs, of which four were investigated in two or more studies. (Figure 13). The pooled AUC (HSROC analysis) for CRP was 0.66 (CI [0.54; 0.79] for sensitivity given specificity and [0.55; 0.74] for specificity given sensitivity) (Figure 14). The HSROC analysis included 33 studies.

Figure 14: Sepsis: HSROC curve for CRP. Blue dots represent individual study results, crosses indicate different cut-offs (in mg/L).



The third biomarker that was assessed was the white blood cell count at 14 different cut-offs and specific subtypes of white blood cells (Figures 15, 16, 17).

Figure 16: Sepsis: ROC plot for WBC (in cells/µL).

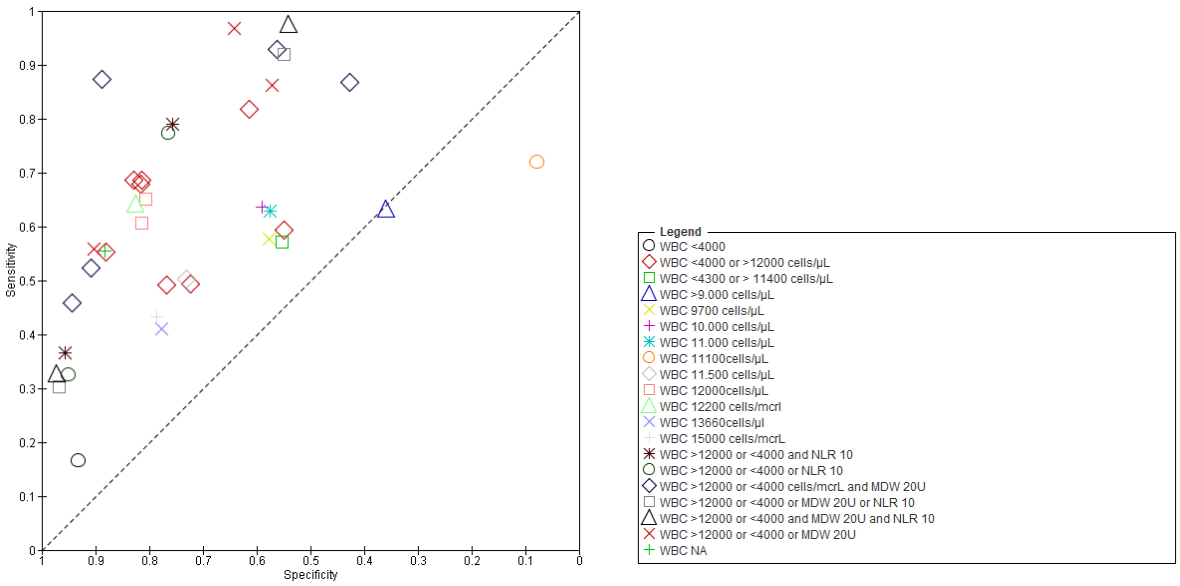
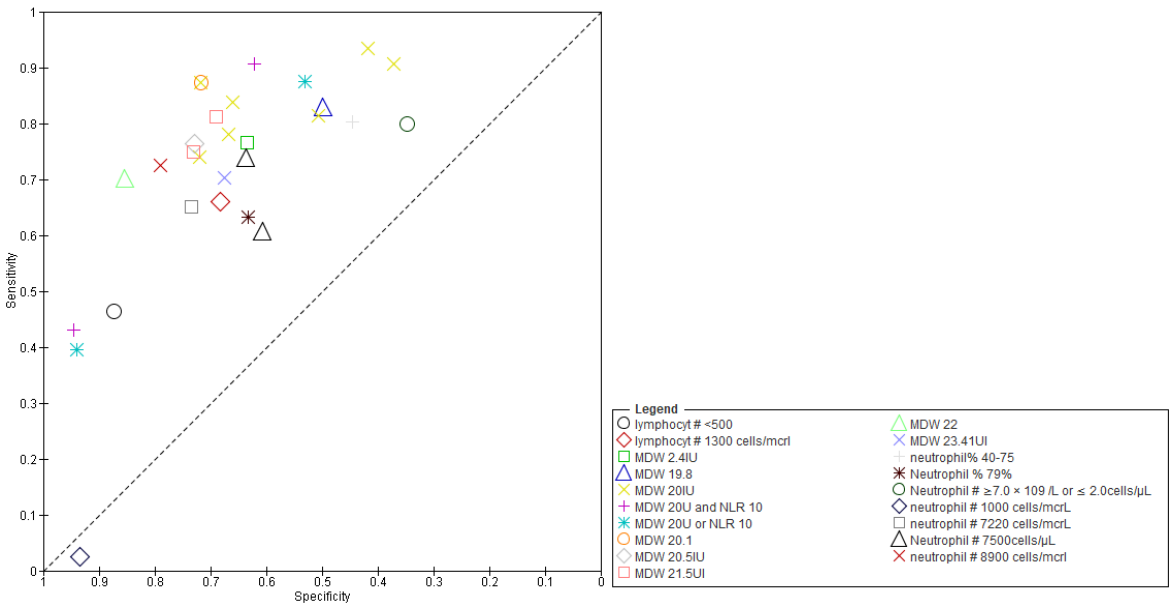
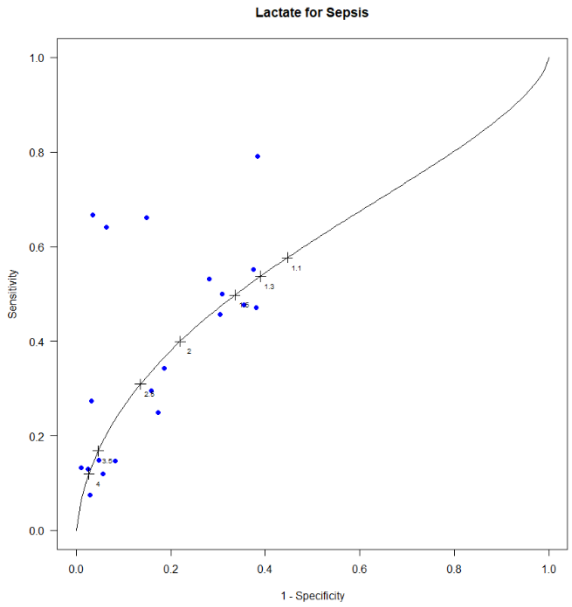


Figure 17: Sepsis: ROC plot for subsets of WBC.



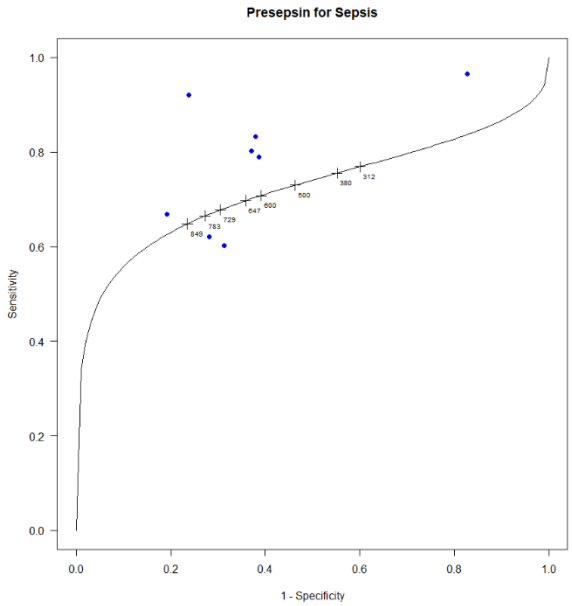
The fourth biomarker that was assessed is lactate at eight different cut-offs, of which four were investigated in two or more studies (Figure 18). The cut off of 2 mmol/L showed a sensitivity of 15% to 79% and a specificity of 62% to 94%.(74,87,88,98,108) The pooled AUC (HSROC analysis) for lactate was 0.59 (CI [0.42; 0.72] for sensitivity given specificity and [0.49; 0.70] for specificity given sensitivity) (Figure 19).

Figure 19: Sepsis: HSROC curve for lactate. Blue dots represent individual study results, crosses indicate different cut-offs (in mmol/L).



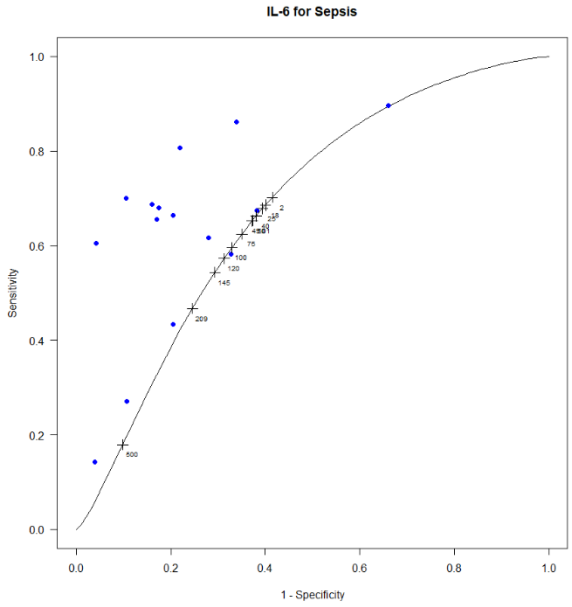
The fifth biomarker that was assessed is presepsin at eight different cut-offs, all investigated in single studies (Figure 20).(92,93,105,118,120,134) The pooled AUC (HSROC analysis) for presepsin is 0.72 (CI [0.37; 0.91] for sensitivity given specificity and [0.58; 0.83] for specificity given sensitivity) (Figure 21).

Figure 21: Sepsis: HSROC curve for presepsin. Blue dots represent individual study results, crosses indicate different cut-offs (in ng/L).



The sixth and last biomarker that was assessed is IL-6 at twelve different cut-offs, of which three were investigated in two or more studies (Figure 22).(64–66,69,82,83,103,110) The pooled AUC (HSROC analysis) for IL-6 was 0.68 (CI [0.56; 0.77[for sensitivity given specificity and [0.54; 0.81] for specificity given sensitivity) (Figure 23).

Figure 23: Sepsis: HSROC curve for IL-6. Blue dots represent individual study results, crosses indicate different cut-offs (in ng/mL).



Discussion

This review focused on serious infections that require prompt treatment or referral to secondary care. Consequently, it is essential to have the ability to reliably rule out these conditions in a primary care setting. To achieve this, a biomarker with high sensitivity is crucial.
We identified twenty-one studies on pneumonia and seventy-seven studies on sepsis, suggesting CRP 30 mg/L has sufficient sensitivity to rule out pneumonia but no biomarker was sufficiently sensitive to rule out sepsis.

Almost half of the studies on pneumonia were performed in a General Practice setting, the rest in the Emergency Department. Only one study on sepsis was performed in a General Practice setting, all others were performed in the Emergency Department. The overall quality of the studies on pneumonia was good, there were no applicability concerns. The overall quality of the studies on sepsis was moderate: twenty-nine studies calculated cut-offs based on the data instead of setting them in advance, overestimating the biomarker's diagnostic performance; six studies did not use an appropriate reference standard, creating a serious risk of bias and an applicability concern; and six studies had a high risk of bias because of their patient selection mechanism.
Our analysis was limited to pneumonia and sepsis, primarily due to an insufficient number of high-quality studies on other infections, such as pyelonephritis or AECOPD. The limited inclusion of COPD related studies may be attributed to the frequent use of case-control designs using stable COPD patients as controls. For pyelonephritis, the underlying reasons for the scarcity of studies with adequate study designs, remain unclear.

Pneumonia

The pooled AUC for PCT was 0.73, whereas the pooled AUC for CRP was 0.80, suggesting that CRP may be more useful in diagnosing pneumonia. However, the risk of bias for CRP was higher than for PCT.
CRP cut-offs below 30 mg/L have sensitivities between 80 and 90%, making it useful to rule out pneumonia, which is needed in primary care. This is already commonly used in standard practice. PCT at a cut-off of 0.8ng/mL has a sensitivity of 60% at best. With lowering cut-off values, the gain in sensitivity seems to be less and less and does not achieve 80%. Knowing that the detection level is located around PCT 0.05-0.02 ng/mL, it seems unlikely that a sensitivity of 80% could ever be reached. This makes PCT less useful to rule out pneumonia.
Other biomarkers were only assessed in single studies, but a few seem promising, as can be seen in Figures 7 and 8. Further research is needed to assess whether these biomarkers could be useful to rule out pneumonia.

Sepsis

Five promising biomarkers were found to rule out sepsis, which we assessed more intensively in the meta-analysis.
Among these, PCT was the most frequently assessed, with an AUC of 0.74. While multiple single studies reported high sensitivity – with 0.5 ng/mL as the most promising result - the pooled analysis showed a stagnation of the sensitivity around 65% that does not increase with decreasing cut-offs. Specificity was higher, especially at a 2 ng/mL cut-off, but in the primary care setting, sensitivity is more important and useful. This, along with high cost, explains why general practitioners do not currently use it.

CRP, alongside with white blood cell count and differentiation, is presently the most commonly used biomarker in general practice to assess severity of infection. The pooled AUC for CRP was 0.66. At a cut-off of 10mg/L a sensitivity of 80% was found, resulting in 20% false negatives. Since sepsis is a diagnosis we should not miss, a cut-off of 10 mg/L cannot safely rule it out.
For presepsin an AUC of 0.72 was found. It would not be applicable in primary care as 312 ng/L, the lowest cut-off we retrieved, demonstrated a sensitivity of only 75%, leaving us with a false-negative rate of 25%. Presepsin has not been studied extensively as only eight studies were found.
Lactate could not achieve a sensitivity we can use in the primary care setting, reaching up to 60% for 1.1 mmol/L. The pooled analysis shows a low AUC of only 0.59. The specificity of a cut-off of 2.5 mmol/L and higher does seem to be very high: >90%. Lactate could be studied for its use to rule in sepsis, but in the primary care setting it seems to be of limited value.
For IL-6, the best cut-off was 2 ng/mL, which yielded a sensitivity of 70%. This level of sensitivity is insufficient for use in primary care, where higher sensitivity is crucial. The pooled AUC was 0.68.

Strengths of the study

The study's large scale is a significant strength, as it enhances the reliability of the findings across diverse studies. Additionally the implementation of strict inclusion and exclusion criteria ensures a well-defined participant group, reducing potential bias. Another strength is our sensitive search strategy, with the use of multiple medical search engines and an extensive query. This offered us a broad amount of studies to further refine in the following analyses. A reference screening was performed as well, gaining additional promising studies. All screenings and analyses were performed by two researchers blinded for each other's results. Conflicts were solved by a third investigator.

Limitations of the study

There is a risk of publication bias, because no follow-up database search was conducted after two years, as we originally planned to do. This could lead to a privation of studies that were published after our search. Some applicability concerns are to be noted in sepsis studies, as described in the results section.
The study was designed to assess the use of biomarkers in general practice, including all studies that took place in primary care. For pneumonia there was an even distribution between studies performed in the general practice and in the emergency department, but for sepsis we only encountered one study in general practice. It should be noted that certain obstacles, mainly regarding availability and cost of tests and delay in receiving the results, are only encountered in the general practice.
The research was funded by the Maurange Fund and the King Baudouin Foundation in Belgium. No conflicts of interest were reported.

Implications for clinical practice

In Dutch pneumonia guidelines a value of CRP <20 mg/L is suggested to rule out pneumonia.(139) This seems to approach our results of a cut-off of 30 mg/L. These guidelines also suggest ruling in pneumonia starting from CRP 100 mg/L, conclusive with our results (specificity >90%). At present, no other biomarkers are used in these guidelines.

Of our investigated biomarkers, only CRP and PCT are momentarily available as a point-of-care test (POCT). POCT is not routinely used due to the limitations of three key barriers: insufficient technological advancements to make tests practical for community use, high associated costs and limited evidence for patient benefits.(140)
The diagnosis or exclusion of both sepsis and pneumonia should never be made solely based on biomarkers. More extensive prediction rules are needed, where biomarkers are combined with clinical parameters and even gut feeling, to higher the diagnostic value even more.
New studies that are aligned with clinical practice are needed.

Implications for research
Further research is needed concerning the role of biomarkers in the diagnosis of pyelonephritis and AECOPD, since the existing literature is limited.
For the diagnosis of sepsis, the biomarker presepsin emerged as a promising biomarker in our study, but it was only investigated in 8 studies. Standardized, multicentric trials are necessary to validate presepsin's diagnostic accuracy and to establish clinically relevant thresholds.
In the context of pneumonia, the review identified a number of biomarkers evaluated only in isolated studies: ESR at 20mm/h, fibrinogen at 4g/L and 5g/L, IL-4 at 9ng/L, IL-5 at 30ng/L, IL-6 at 15 ng/L and LBP at 10µg/mL and 20µg/mL. Their preliminary findings are encouraging and point toward a rich area for exploration. Further research is needed, as it could reveal new opportunities for improving diagnosis in infectious diseases.

Conclusion

Serious infections, such as pneumonia and sepsis, pose significant diagnostic challenges due to their nonspecific symptoms and the critical need for timely treatment. Our systematic review confirms the potential role of biomarkers in improving diagnostic accuracy and guiding clinical decision-making. The review demonstrates the clinical significance of CRP over PCT in ruling out pneumonia, showing cut-offs that approximate the values offered in contemporary guidelines to diagnose or rule out pneumonia. For sepsis a meta-analysis was performed using CRP, PCT, lactate, IL-6 and presepsin. CRP demonstrated the strongest overall evidence base for ruling out sepsis. Presepsin showed the most promising performance but was evaluated in fewer studies, requiring further research. It should be mentioned that many biomarkers were only investigated in a limited number of studies, thus creating some difficulty in assessing their clinical applicability.

Further investigation of biomarkers for other serious infections, such as pyelonephritis and COPD exacerbations, as well as more extensive research for less investigated biomarkers (such as presepsin), could enhance early diagnosis and improve patient outcomes.

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Appendices

Table 1: Search strategy in Medline, using the PubMed interface

P	
I	“Blood Cell Count”[Mesh] OR “Blood cell count”[tiab] OR "white blood count"[tiab:~3] OR "WBC count"[tiab] OR “full blood count”[tiab:~3] OR “Whole blood count”[tiab] OR “FBC”[tiab] OR “Clinical Laboratory Techniques”[Mesh:NoExp] OR “laboratory technique*”[tiab] OR "laboratory technic*"[tiab] OR "technical investigation*"[tiab] OR “Blood Chemical Analysis”[Mesh] OR “Blood Chemical Analys*”[tiab] OR “Hematologic tests”[Mesh] OR “Hematological test*”[tiab] OR “Haematological test*”[tiab] OR “Hematologic test*”[tiab] OR “Haematologic test*”[tiab] OR “Rapid Diagnostic Test*”[tiab] OR “Liver function tests”[Mesh] OR "liver test*"[tiab] OR "liver function*"[tiab] OR "hepatic function*"[tiab] OR "hepatic test*"[tiab] OR “Lactic acid”[Mesh] OR “Lactic acid”[tiab] OR “Lactate”[tiab] OR “Biomarkers"[Mesh:NoExp] OR “Biomarker*"[tiab] OR “marker*"[tiab] OR “Inflammation mediators”[Mesh] OR “Inflammation mediator*”[tiab] OR “Acute-Phase Proteins”[Mesh] OR “Acute phase protein*”[tiab] OR “Acute phase reactant*”[tiab] OR "Point-of-Care Testing"[Mesh] OR “Point of care test*”[tiab] OR “POCT”[tiab] OR "POC test*”[tiab] OR “Near patient test*”[tiab] OR “Rapid test*”[tiab] OR “Bedside technolog*”[tiab] OR “Bedside test*”[tiab] OR “I-stat”[tiab] OR “Istat”[tiab] OR “Afinion”[tiab] OR “Blood test*”[tiab] OR “Blood analys*”[tiab] OR “C-Reactive Protein”[Mesh] OR “C-reactive protein”[tiab] OR “CRP”[tiab] OR “presepsin protein, human”[Supplementary Concept] OR “Presepsin”[tiab] OR “Procalcitonin”[Mesh] OR “Procalcitonin”[tiab] OR “PCT”[tiab] OR "Calcitonin"[Mesh] OR "Calcitonin"[tiab] OR “Sedimentation rate”[tiab] OR “SuPAR”[tiab] OR “soluble urokinase Plasminogen Activator Receptor”[tiab] OR ”PTX3 protein”[Supplementary Concept] OR “Pentraxin 3”[tiab] OR “PTX”[tiab] OR "PTX3"[tiab] OR "PTX-3"[tiab] OR ”mid-regional pro-adrenomedullin, human”[Supplementary Concept] OR “mid-regional pro-adrenomedullin”[tiab] OR “interleukins” [Mesh] OR “interleukin*”[tiab] OR “IL6”[tiab] OR “IL-6”[tiab] OR “heparin-binding protein”[tiab] OR “Neutrophil-to-lymphocyte ratio”[tiab] OR “NLR”[tiab] OR “platelet-to-lymphocyte ratio”[tiab] OR “PLR”[tiab] OR “Neutrophil CD64”[tiab] OR “Neutrophil CD-64”[tiab] OR “nCD64”[tiab] OR “nCD-64”[tiab] OR “MR-pro-ANP”[tiab] OR “monocyte human leukocyte antigen-DR”[tiab] OR “mHLA-DR”[tiab] OR “copeptins”[Supplementary Concept] OR “Copeptin*”[tiab] OR “CT-pro-AVP”[tiab] OR ”fibrin fragment D”[Supplementary Concept] OR “fibrin fragment D”[tiab] OR “D-Dimer”[tiab] OR “Progranulins”[Mesh] OR “Progranulin*”[tiab] OR “YKL-40”[tiab] OR "YKL40"[tiab] OR “neutrophil lipocalin”[tiab] OR “High Mobility Group box-1”[tiab] OR “HMGB1”[tiab] OR "midregional pro-atrial natriuretic peptide, human" [Supplementary Concept] OR "MR-proANP"[tiab] OR "midregional pro-atrial natriuretic peptide"[tiab] OR "BNP"[tiab] OR “NT-pro-BNP” [tiab] OR "Triggering Receptor Expressed on Myeloid Cells-1"[Mesh] OR "TREM1 protein, human"[Supplementary Concept] OR “Triggering Receptor Expressed on Myeloid Cells 1”[tiab] OR “TREM”[tiab] OR "sTREM"[tiab] OR "Macrophage Migration-Inhibitory Factors"[Mesh] OR "Macrophage Migration-Inhibitory Factor*"[tiab] OR "Matrix Metalloproteinases"[Mesh] OR "Matrix Metalloproteinase*"[tiab] OR "MMP*"[tiab] OR "lipopolysaccharide-binding protein"[Supplementary Concept] OR "lipopolysaccharide-binding protein*"[tiab] OR "LBP*"[tiab] OR “kallistatin”[Supplementary Concept] OR “Kallistatin”[tiab] OR “Serpin*”[tiab] OR “Tumor Necrosis Factors"[Mesh] OR “tumor necrosis factor”[tiab] OR “tumour necrosis factor”[tiab] OR “TNF”[tiab] OR "TNFalpha"[tiab] OR "TNFa"[tiab] OR “Albumins"[Mesh:NoExp] OR “Albumin*”[tiab]
R	
T	“Pneumonia”[Mesh:NoExp] OR “Pneumonia, Bacterial”[Mesh:NoExp] OR "Pneumonia, Viral"[Mesh:NoExp] OR “Pneumonia”[tiab] OR “Acute exacerbation COPD”[tiab:~3] OR “Acute exacerbation chronic obstructive pulmonary disease”[tiab:~3] OR “AECOPD”[tiab] OR "AE COPD"[tiab] OR “Bacteremia”[Mesh] OR “Bacteremia”[tiab] OR “Bacteraemia”[tiab] OR "septicemia"[tiab] OR "septicaemia"[tiab] OR “Shock, Septic”[Mesh] OR “Septic shock”[tiab] OR “sepsis”[tiab] OR “Pyelonephritis”[Mesh:NoExp] OR “Pyelonephritis”[tiab]
S	“General Practice”[Mesh] OR “General Practitioners”[Mesh] OR “general practi*”[tiab] OR “family practi*”[tiab] OR “family doctor*”[tiab] OR “family physician*”[tiab] OR “Gp”[tiab] OR "GPs"[tiab] OR “primary care centre*”[tiab] OR “primary care center*”[tiab] OR “primary care setting*”[tiab] OR “Ambulatory care”[Mesh] OR “Ambulatory care facilities”[Mesh] OR “Ambulatory”[tiab] OR “Outpatients”[Mesh] OR “Outpatient*”[tiab] OR “Out-patient*”[tiab] OR “Emergency Service, Hospital”[Mesh] OR “Emergenc*”[tiab]

Table 2: Study characteristics

Study_name	Target_disease	index tests	Age_group	reference standard	setting; country	inclusion criteria	exclusion criteria	design	population (N, median age, prevalence)
Ahmadinejad 2009	sepsis, ns	PCT	adults	positive bloodculture	ED; Iran	All adult patients with SIRS	mechanical trauma, severe burns, heat stroke, cancer, surgical trauma, age less than 12 years, and those who received antibiotic therapy for more than 48 hours before study	prospective	120; 49.1Y; 59.2%
Azijli 2022	Bacteraemia	PCT	adults	positive bloodculture	ED; Netherlands	18 years and older with a blood culture and a viral test in ED	blood culture, PCT or viral test not available	prospective	546; 64Y; 8.6%
Bolanaki 2021	Sepsis, ns	PCT	adults	sepsis-3	ED; Germany	age ≥ 18 years + qSOFA score of at least 1	acute trauma, acute ST-elevation myocardial infarction, suspected stroke, admitted for palliative care with a life expectancy of less than 1 month, pregnancy, referrals from other hospitals following prior in-hospital treatment	prospective	741; 68Y; 27.2%
Caterino 2004	Bacteraemia	PCT, abnormal WBC	adults >=65Y	positive bloodculture	ED	ED patients aged >65 years in whom blood cultures were	antibiotic use within the preceding 48 hours	prospective	108; 76Y; 13%
Chirouze 2002	Bacteraemia	PCT	adults	positive bloodculture	ED; France	fever	<18Y, hospital-acquired infection, transfer from another medical institution	prospective	165; 57Y; 13%
Contenti 2019	Sepsis or septic shock	CRP, PCT, presepsin, lactate	adult	sepsis-3	ED; France	>18j, >/= 2 SIRS criteria, suspected infection, arterial lactate	Terminal kidney failure, active malignancy with chemotherapy, palliative care	prospective	359; 70y; 63.5%
Crouser 2020	Sepsis, ns	MDW, abnormal WBC	adults	sepsis-2	ED; US	18-89Y presenting to the ED + CBC with differential	inadequate blood samples, discharged within 12h, prisoners, prior study enrollment	retrospective	2158; mean age 60y; 17.8%
Crouser 2017	Sepsis, ns	MDW, WBC, MDW+WBC	adults	sepsis-2	ED; US	18-90Y + CBC within 24h of admission to the ED	none	prospective	1320; not specified; 7.4%
Crouser 2019	Sepsis, ns	WBC, WBC+MDW, MDW	adults	sepsis-2	ED; US	18-89Y + CBC with differential upon presentation to the ED	inadequate bloodsamples, readmission tot ED or discharged from ED within 12h, prisoners, prior study enrollment	prospective	2158; not specified; 17.8%
	Sepsis (sepsis-3 criteria)	MDW		sepsis-3					2158; not specified; 11.3%
DalPonte 2018	Sepsis, ns	CD64	adults	sepsis-2	ED; Brazil	SIRS criteria	<18Y, refusal to participate, discharge or death before 48h of admission	prospective	109; 61Y; 41.3%
deGuadianaRomualdo 201	Sepsis, ns	PCT, presepsin, CRP	adults	sepsis-3	ED; Spain	>14Y with suspected infection +body fluid cultures drawn at time of admission	<14Y, immunocompromised stage, terminal stage of disease and pregnancy	prospective	223; 69Y; 31.4%
deHond 2022	Sepsis, ns	PSP	adults	MEWS ≥5 + probable or definite infection	ED; Netherlands	adults presenting to the ED with suspicion of infection	none	prospective	156; mean age 60Y; 16.7%
Deitcher 1993	Bacteraemia	Cross-linked fibrin degradation products	adults	positive blood culture	ED; US	adult patients from whom blood samples were drawn because of suspected bacteriemie	none	prospective	100; 55Y; 21%
Freund 2012	Sepsis	lactate, PCT	adults	sepsis-2	ED; France	>15Y presenting to the ED with a suspected diagnosis of infection who had both lactate and PCT sampled in the ED	none	prospective	462; mean age 64Y; 61.3%
	Severe sepsis								462; mean age 64Y; 25.3%
	Septic Shock								462; mean age 64Y; 2.2%
Gaini 2006	sepsis + severe sepsis	PCT, CRP, LBP, IL6	adults	sepsis-2	ED; Denmark	suspected diagnosis of infection as judged by the referring physician and blood cultures drawn at the time of admission	<18Y, earlier participation in the study or prior hospitalisation within 7 days before admission	prospective	174; 64Y; 42.8%
Gámez-Díaz 2011	Sepsis, ns	CD64, HMGB-1, s-TREM-1	adults	expert consensus	ED; Colombia	adult patients with one of the following: suspected or confirmed infection, fever of unknown origin, delirium or encephalopathy of unknown origin, or acute hypotension	refusal to participate, antimicrobial treatment received at another medical institution immediately before admission, medical decision to treat the patient ambulatory or in a different institution within 24h after admission, homeless or inability of the patient to follow up, previous participation in the same study	prospective	631; 51Y; 65.9%
GarcíadeGuadianaRomual	Sepsis, ns	LBP, PCT, CRP	adults	sepsis-3	ED; Spain	Patients with suspected infection + cultures collected at the time of admission	age less than 18 years old, evidence of an immunocompromised state (e.g. malignancy), terminal stage of disease and pregnancy	prospective	102; 70.5Y; 48%
GarcíadeGuadiana-Romua	Sepsis or septic shock	PSP, sCD25, PCT	adults	sepsis-3	ED; Spain	suspicion of infection and clinical request of body fluid cultures drawn at the time of admission	age less than 14 years old, evidence of an immunocompromised stage (e.g. malignancy), terminal stage of disease and pregnancy.	prospective	152; 66Y; 30.9%
Gille-Johnson 2012	Bacteraemia	CRP, PCT, bilirubin, D-dimer, neutrophils, platelet#, urea, lactate, IL-6, LBP, WBC	adults	positive bloodculture	ED; Sweden	at least 1 set of blood cultures drawn on admission	age below 18 y and prior participation in the study.	prospective	404; 61Y; 16.8%
Hausfater 2007	Bacteraemia	PCT	adults	positive bloodculture	ED; France	oral temperature >38.5°C	<15Y	prospective	243; 56Y; 17%
Hausfater 2021	Sepsis, ns	MDW, WBC, PCT, CRP, MDW+WBC, MDW+PCT, MDW+CRP, MDW+WBC+CRP, MDW+WBC+PCT	adults	sepsis-2	ED; France and Spain	consecutive adult patients (18–89 years) presenting to the ED and who had a CBC-DIFF ordered	Patient age, informed consent, previously enrolled, subject whitout social security, PCT and CRP not performed by protocol and operator error, discharged from ED < 4 hrs, CBC-Diff not orderd upon presentation, patient withdrew from study, subject under custody or guardianship, LDW results not valid: flagged or > 2 hrs TAT (turn around time)	prospective	1517; 64; 17.1%
	Sepsis, ns			sepsis-3					1517; 64; 9.5%
Hicks 2014	Sepsis, ns	PCT	adults	sepsis-2	ED; USA	18 years or older with signs and symptoms of infection, blood culture acquisition	pregnant, incarcerated, and non-English speaking, unwilling/unlikely to be reachable for a planned 30-day follow-up telephone call. Patients who had liver disease, hepatitis, or reported alcohol consumption of more than two drinks per day for at least 6 months	prospective	66; 58; 28.8%
Hoenigl 2013	bacteraemia	suPAR	adults	positive bloodculture	ED; Austria	>18Y, clinical suspicion of bacteraemia by the attending physician and consecutive order of bloodcultures, fulfillment of SIRS criteria, no antibacterial therapy last 5 days, informed consent	<18Y, no order of blood cultures at emergency department, no fulfillment of SIRS criteria, antibacterial therapy last 5 days	prospective	132; 67; 41.6%
Ishikura 2014	Sepsis, ns	presepsin, PC activity, AT activity, TM, platelet#, PT-INR, D-dimer, PCT, IL-6, CRP, WBC	adults	ACCP/SCCM consensus conference sepsis criteria	ED; Japan	aged ≥18 years, one or more SIRS criteria present	Patients who lacked biomarker data or clinical manifestations	prospective	82; 72.5Y; 52.4%

Study_name	Target_disease	index tests	Age_group	reference standard	setting; country	inclusion criteria	exclusion criteria	design	population (N, median age, prevalence)
Jaimes 2013	Sepsis, ns	CRP, DD, PCT,	adults	expert consensus	ED; Colombia	hospitalized in the ER within 24 hours before admission to the study, >18 years, at least one of the following causes as the main admission diagnosis to the hospital: a) any kind of infectious disease (confirmed or suspected), b) fever of unknown origin, c) delirium or any kind of encephalopathy of unknown origin or d) acute hypotension not explained by hemorrhage, myocardial infarction, stroke or heart failure.	refusal to participate, antimicrobial treatment received at another medical institution immediately before admission to the study, medical decision to treat the patient ambulatory or in a different institution within 24 hours after admission, homeless or inability of the patient to follow up, previous participation in the same study.	prospective	765; 51.4Y; 66%
Jekarl 2013	bacteraemia	PCT, IL-6, CRP, ESR, WBC	adults	sepsis-2	ED; South Korea	SIRS in ED	evidence of immunocompromised state (eg malignancy, HIV infection), visited the hospital of discharged from the hospital in the last 14 days, adminstered antibiotics before admission	prospective	177; 51.5Y; 35%
	severe sepsis/septic shock	PCT, IL-6, CRP, ESR, WBC	adults	sepsis-2	ED; South Korea	SIRS in ED	evidence of immunocompromised state (eg malignancy, HIV infection), visited the hospital of discharged from the hospital in the last 14 days, adminstered antibiotics before admission	prospective	177; 51.5Y; 44%
Jekarl 2015	sepsis, ns	PCT, CRP, ESR, WBC, IG, IL-1, IL-2, IL-4, IL-5, IL-6, IL-9, IL-10, IL-12, IL-13, IL-17, IL-22, TNF, IFNgamma	adults	sepsis-2	ED; South Korea	>18Y, SIRS in ED	evidence of immunocompromised state (eg malignancy, HIV infection), visited the hospital of discharged from the hospital in the last 14 days, adminstered antibiotics 14 days before admission	prospective	127; 59.2Y; 76%
Jekarl 2019	Sepsis, ns	PCT, CRP, ESR, WBC	adults	sepsis-3	ED; Korea	Signs and symptoms of suspected infection	Immunocompromised state or evidence of viral infection	prospective	248; 70.1Y; 74.6%
Karon 2017	Sepsis, ns	lactate, neutrophil#, neutrophil%, IG #, IG%, WBC, PCT	adults	ACCP/SCCM consensus conference sepsis criteria	ED; USA	sepsis panel ordered while in ED admission, suspucion of sepsis	None	prospective	501; unknown; 46.7%
Katsaros 2022	Sepsis, ns	HBP	adults	sepsis-3	ED; Greece	adults with suspected infection and presence of at least one of the following: core temperature > 38°C or <36°C; heart rate > 90 bpm; respiratory rate > 20/min and self- reported fever/chills	None	prospective	371; mean 62.4Y; 44.7%
Kofoed 2007	Sepsis, ns	CRP, PCT, neutrophil#, MIF, sTREM-1, suPAR, 3-marker score, 6-marker score	adults	ACCP/SCCM consensus conference sepsis criteria	ED; Denmark	Adult patients, < 24 hours admitted, fulfilled at least two SIRS criteria	Admission > 24 hours, referral from other departments/hospitals, no written consent, age < 18 years, refusal to participate	prospective	151; 56Y; 64%
Lai 2010	Sepsis, ns		>65	sepsis-2	ED; Taiwan	patients aged 65 and older who fulfilled the criteria for SIRS (SIRS was defined as the presence of two or more of tachycardia; tachypnea or hypoxia; hypothermia or hypothermia; and leukocytosis, leukopenia, or bandemia.)	missing data or loss of follow-up and preexisting thyroid disease	prospective	262; 77.2Y; 18%
Lee 2012	Bacteraemia	CPR, blood urea nitrogen, platelet#	adults	positive bloodculture	ED; Taiwan	febrile adult patients visiting the ED, aged 18 years or older, and a febrile duration of less than 4 weeks.	patients with consciousness alteration or without verbal responses	prospective	454; 54.1Y; 16.3%
Lee 2012 b	Bacteraemia	WBC, Hb, platelets, BUN, creatinin, PH/(arterial ratio	adults	positive bloodculture	ED; Taiwan	temperature >38.0°C, >18Y, febrile duration <1 week	consciousness alteration, no verbal responses, hospitalisation within last 30 days, residents of nursing facilities, fungemia or mycobacteremia	prospective	396; 53.8Y; 15%
Li 2022	Sepsis, ns	MDW, PCT, MDW+WBC	adults	sepsis-3	ED; Taiwan	≥20 years, fever or altered mental status or hypotension, or dyspnea, and Complete blood cell count with diferential testing (CBC/DC)	Subjects previously enrolled in this study, previous antibiotic treatment, Pregnant women, MDW result not reported , no informed consent.	prospective	402; 63.7Y; 13%
Lindvig 2014	Bacteraemia	CRP, leucocyte#, neutrophil#, lactate, creatinine	adults	positive bloodculture	ED; Denmark	>15y + bloodculture ordered	obvious cardiological, chronic oncological, haematological, nephrological or actue hemorrhagic patients, parturient women and pediatric patients.	prospective	5499; 66Y; 7.5%
Lin 2000	Bacteraemia	IL-6, IL-8	adults	positive bloodculture	ED; China	>/=2 SIRS criteria	pregnancy, neoplasia, hepatitis, acquired immuno-deficiency syndrome, severe burns, uncontrolled major hemorrhage, taking immuno-suppressive medications, NSAID, drugs or antibiotics	prospective	100; 44.5Y mean; 23%
Lin 2023	Sepsis, ns	WBC, NLR, PLR, CRP, MDW	≥60years	sepsis-2	ED; Taiwan	>60y, suspection of infection, complete workup for sepsis	no confirmed diagnosis of infectious disease, incomplete workup of sepsis	prospective, nested case-controle	2610; 75.4Y; 20%
Ljungström 2017	Sepsis	PCT, CRP, lactate, NLR		sepsis-2	ED; Sweden	>18y, suspicion community-onset sepsis	no informed consent	prospective	1572; 71Y; 42%
Ljungström 2017	Sepsis			sepsis-3					1572; 71Y; 35.6%
Ljungström 2017	Severe sepsis/septic			sepsis-2					1572; 71Y; 10.8%
Loots 2022	Sepsis, ns	CRP, lactate, PCT, Hs-TnI, NT-proBNP, creatinine, urea, PSP	adults	sepsis-3	GP; Netherlands	>18y, fever or confusion of deterioration or otherwise suspected of severe infection	non-infectious cause of acute complaints, hospitalisation <7d before home visit, condition that requires secondary care assessment, terminal illness	prospective	336; 80Y; 41.9%
Lucchiari 2014	Sepsis or septic shock	presepsin, PCT	adults	ACCP/SCCM consensus	ED; Italy	suspected sepsis, >2SIRS criteria , blood test	<18y, incapability to give informed consent, clearly different diagnosis	prospective	189; 64Y; 56%
Malinovska 2022	Sepsis	MDW, WBC, NLR, MDW and WBC, MDW or WBC, MDW and NLR, MDW or NLR, WBC and NLR, WBC or NLR	adults	sepsis-3	ED; USA	adult patients who had a CBC collected within 6 hours of ED arrival	missing a valid MDW, MDW sample analysed >2 hours after blood collection, missing other CBC paremeters (WBC count, neutrophils, lymphocytes) within 6h of arrival, repeat visits	prospective	7952; 50Y; 1.7%
Malinovska 2022	Septic shock								7952; 50Y; 2%
Moscovitz 1994	Bacteraemia	IL-6	adults	positive blood culture	ED; USA	presumptive diagnosis of bacteremia (defined by the decision of the physician to perform blood cultures) and at least 1 of the following: temperature instability, hypotension, leucocytosis, metabolic acidosis or physical findings indicative of focal infection	neoplastic disease, AIDS, pregnancy, currently taking immunosuppressive drugs or antibiotics	prospective	100; 51Y; 18%

Study_name	Target_disease	index tests	Age_group	reference standard	setting; country	inclusion criteria	exclusion criteria	design	population (N, median age, prevalence)
Nestor 2021	Bacteraemia	NLR, lactate, CRP	adults	positive bloodculture	ED; Sweden	adults presenting to the ED who were subjected to blood culture due to suspected bacteremia	disapproval of study participation	prospective	484; 64.6Y mean; 17%
Ognibene 2022	Sepsis, ns	CRP, MDW, PCT	adults	sepsis-3	ED; Italy	clinical presentation of suspected sepsis	positive for SARS-CoV-2	prospective	308; 61Y; 25%
Oh 2009	Severe sepsis + septic shock	PCT	adults	ACCP/SCCM consensus conference sepsis criteria	ED; Korea	patients with suspected diagnosis of infection and who meet the SIRS criteria	SIRS of an noninfectious origin such as trauma, pancreatitis, burn, hemorrhagic shock, and immune-mediated injury	prospective	80; 65.6Y mean; 41%
Olander 2023	Sepsis, ns	glucose, lactate	adults	sepsis-3	ED; Sweden	patients >16Y assessed by the rapid triage and treatment system as having red, orange, yellow or green levels if their respiratory rate >22 breaths/minute	received care at another ambulance service, incorrect registration in the database, missing social security number, cardiac arrest/death on arrival, plasma glucose not recorded, admitted to another hospital where data were not retrievable, and not admitted for in-patient carre and remained at the scene, status epilepticus	prospective	1057; 75Y mean; 58%
O'Neal 2021	Sepsis, ns	PCT	adults	sepsis3	ED; USA	2 or more modified SIRS criteria or clinician's order for culture of a body fluid	expected palliative course, history of hematologic disorders, cytotoxic chemotherapy within 3 months of the ED encounter, prisoners, patients transferred from other acute care facilities, unwilling or unable to consent	prospective	266; 57Y; 18%
Paul 2023	Sepsis, ns	NGAL	adults	positive bloodculture	ED; Italy	more than 18 years of age presenting with fever and SIRS score of 2 or more requiring hospitalization	prolonged fever more than 2 weeks, intravenous antibiotic administration 48 hours prior to admission, hospitalization or surgical intervention in the preceding 2 weeks, Human Immunodeficiency Virus (HIV) infection, and chronic kidney disease.	prospective cohort study	100; 50.7Y mean; 37%
Polilli 2022	Sepsis, ns	MDW, WBC, neutrophil#, lymphocyt#, platelet#, CRP	adults	sepsis-2	ED; Italy	adult patients with an available Complete Blood Count (CBC) analysis, admitted for any reason to the ED	discharged from ED within 12 h,pregnant, leaving the ED before discharge, with incomplete clinical or laboratory data, or with missing MDW after CBC analysis	prospective	2742; 62.9Y mean; 10%
Poz 2022	Sepsis, ns	MDW, CRP, WBC, neutrophil#, glucose, lactate, MDW or WBC, MDW and WBC	adults	sepsis-2	ED; Italy	adult patients for whom a complete blood count differential (CBC-Diff) was requested as part of the standard clinical practice.	Patients discharged from the ED within 4 h, patients previously enrolled in the study; patients with non-reportable MDW	prospective cohort	985; unknown; 6%
Quick 2000	Bacteraemia	D-dimer	adults	positive bloodculture	ED; USA	All patients having a blood culture drawn	contaminated bloodculture, lost data	prospective	265; 43.3Y; 9%
Romualdo 2014	Bacteraemia	CRP, PCT, presepsin	adults	positive bloodculture	ED; Spain	Adult, at least two or the SIRS criteria, clinical suspicion of bacteremia, blood culture order	age less than 18 years old, pregnancy	prospective	226; 67Y mean; 16%
Ruangsomboon 2020	Sepsis + Septic shock	presepsin, PCT, CRP, presepsin+PCT, presepsin+CRP, PCT+CRP	>=75 years	sepsis-3	ED; Thailand	age ≥ 75 years, suspected sepsis	hemocultures taken before ED arrival	prospective	250; 83.4Y mean age; 56%
	Septic shock								250; 83.4Y mean; 36%
Schuetz 2011	Sepsis, ns	E-selectin, ICAM-1, VCAM-1, PAI-1, VEGF, sFLT-1	adults	expert consensus	ED; USA	>17 years of age, at least one systolic blood pressure (SBP) measurement of <100 mm Hg during the visit in the ED	None	prospective	161; 60Y mean; 43%
Shankar-Hari 2018	Sepsis, ns	CD15, CD24, CD35, CD64, CD132, CD11b, CD274, CD279, CD312, HLA-DR, CD8 Tcells CD279, neutrophil CD24+, neutrophil CD279, CRP, PCT	adults	sepsis-3	ED; UK	Age ≥16 years (≥18 years in England), SIRS criteria met, clinical suspicion of sepsis, no clinical suspicion of severe sepsis or septic shock at the time of enrolment and enrolled within 12 hours of hospital (ED) presentation	patients with acute pancreatitis, haematological malignancy, chemotherapy in the past 2 weeks, myelodysplastic syndromes, known neutropenia, HIV infection, viral hepatitis infection, pregnancy, bloodtransfusion > 4 units in the past week, oral corticosteroids for > 24 h prior to enrolment, or a decision not to have active therapy/for palliative care	prospective	272; 62.1Y; 51%
Shapiro 2009	Severe sepsis	NGAL, IL-1Ra, PC, MIP-3, CRP, TNF-R1a, BNO, PGRP-S, D-dimer, sepsis score	adults	ACCP/SCCM consensus conference sepsis criteria	ED; USA	adult ED patients, a suspicion of infection by the treating clinician or a serum lactate level ¹2.5 mmol/L; two of four criteria for the systemic inflammatory response syndrome	pregnancy, DNR status, cardiac arrest.	prospective	971; 54.9Y mean; 52%
Shim 2019	Bacteraemia	WBC PCT, SB PCT, lactate, CRP	adults	positive bloodculture	ED; Korea	a febrile sense, suspected infection, underwent serum PCT testing	under 18 years, pregnant or had limited life expectancy due to chronic diseases.	prospective	199; 67.1Y; 66%
Singer 2014	All sepsis	lactate	adults	ACCP/SCCM consensus conference sepsis criteria	ED; USA	suspicion of infection, at least two of the criteria for systemic inflammatory response syndrome	None	prospective	258; 64Y mean; 81.5%
	Severe sepsis + septic shock								258; 64Y; 42.2%
	Septic shock								258; 64Y; 11.6%
Singla 2022	Sepsis, ns	MDW, neutrophil#, WBC	adults	sepsis-2 and 3	ED; India	critically ill adult patients	need of oxygen (severe acute respiratory infections)	prospective	148; 48.3Y; 26%
Su 2011	Bacteraemia	AST, BUN, CRP, PCT? WBC, PLT#, lymphocyt#, Na, Bands	adults	positive bloodculture	ED; Taiwan	aged 15 years or older, who had at least two sets of blood cultures from separate site	admission of antibiotics before hemoculture, active thyroid cancer	prospective	558; 60.8Y; 15%
Tan 2016	Sepsis, ns	CD64, sPLA2-IIA	adults	sepsis-2	ED; Malaysia	18+, suspected sepsis or 2 or more SIRS criteria, systolic blood pressure (SBP) less than 90mmHg after a minimum of 30ml/kg crystalloid fluid bolus	AB for more than 3 days, oncology diseases, passed away during the period of recruitment, transferred to other hospitals	prospective	51; 53.7Y; 82%
Tromp 2012	Bacteraemia	PCT, IL-6, LBP, CRP, PCT	adults	positive bloodculture	ED; Netherlands	16 or older, suspected infection, 2 or more clinical signs of sepsis (T>38,3 or <36, HR>90/min, RR>20/min, chills, altered mental status, SBP <90 mmHg, MAP <65mmHg, hyperglycemia without DM)	None	prospective	342; 59Y; 16%
Tsalik 2012	Bacteraemia	PCT, IL-6, CRP	adults	sepsis-2	ED; USA	known/suspected infection obv clinical data at the time of screening + 2 or more SIRS criteria within a 24-hour period	<18y, terminal condition, HIV/AIDS with CD4 count <50 cells/ml, receiving AB for a condition unrelated, participating in an ongoing clinical trial	prospective	336; 52Y; 21.2%
Tsalik 2012	Sepsis + Severe sepsis								336; 52Y; 73.5%
Tudela 2010	Bacteraemia	leucocytosis, bands, neutropenia, CRP, PCT	adults	positive bloodculture	ED; Spain	suspected infection + hemocultures	None	prospective	275; 67.7Y; 13.5%

Study_name	Target_disease	index tests	Age_group	reference standard	setting; country	inclusion criteria	exclusion criteria	design	population (N, median age, prevalence)
Uusitalo-Seppälä 2013	Severe sepsis	PTX3, PCT, CRP	adults	sepsis-2	ED; Finland	suspection of infection by clinician, blood sample taken	incomplete data, SIRS and organ dysfunction but no bacterial infection	prospective	537; 64Y; 9.1%
Uusitalo-Seppälä 2012	Severe sepsis	suPAR	adults	sepsis-2	ED; Finland	suspection of infection by clinician, blood sample taken	incomplete data, SIRS and organ dysfunction but no bacterial infection	prospective	539; 61Y; 91%
Uusitalo-Seppälä 2011	Severe sepsis	IL-6	adults	sepsis-2	ED; Finland	suspection of infection by clinician, blood sample taken	None	prospective	539; 61Y; 91%
Uusitalo-Seppälä 2012b	Severe sepsis	BPI, PLA2-IIa, WBC	adults	sepsis-2	ED; Finland	suspicion of infection, blood samples taken	incomplete data, SIRS and organ dysfunction but no bacterial infection	prospective	525; 64Y; 9.3%
Velly 2021	Sepsis, ns	HLADR-PCT-IL6, IL6-PCT-CRP, HLADR-PCT, HLADR-IL6, HLADR-CRP, HLADR-MERTK	adults	sepsis-2	ED; France	>/=18y & 1 of the following criteria:Temperature >38 °C, chills, marbling, systolic blood pressure <90 mmHg or mean arterial pressure <70 mmHg, cough, purulent sputum, unilateral thoracic altered sound on auscultation, abdominal defence or contracture, monoarthritis, unilateral red swelling leg, unilateral facial oedema, urine test strip positive for leukocytes and/or nitrite. white blood cells count <4000 or > 12.000/mm3.	< 18 years, patients with no social insurance, homeless people without possible follow-up, pregnant women, those who refuse to participate, prisoners, and patients with dementia and/or cognitive impairment precluding informed consent.	prospective	291; 60Y; 24%
Velly 2021		creatinine-HLADR, creatinine, hyaluronan-HLADR		sepsis-3					291; 60Y; 5%
Visveswari 2019	Sepsis, ns	CRP, PCT, neutrophil%, NLCR, lactate, WBC, NLCR + CRP +Neutrophil%, NLCR + CRP + WBC, NLCR + WBC + Neutrophil%, CRP + WBC + Neutrophil%, NLCR + CRP, NLCR + Neutrophil%, CRP + Neutrophil%, WBC + CRP, WBC + Neutrophil%	adutls	sepsis-2	ED; Singapore	adults presenting to the ED with complaints suggestive of an infection	<21Y, known pregnancy, prisoners, DNR-status, primary diagnosis of trauma/burns/active seizure/acute cerebral vascular accident/acute coronary syndrome/status asthmaticus/major cardiac arythmias/active gastrointestinal haemorrhage/drug overdose, requierment for immediate surgery, active chemotherapy, haematological malignancy, inability tot provide informed consent and comply with study requirements	prospective	126; 66Y; 48%
Wallgren 2020	Sepsis, ns	lactate, suPAR, HBP, glucose	adults	sepsis-3	ED; Sweden	adult non-trauma ambulance patients considered to suffer from a new onset infection	lack of written consent, trauma other than falls at home, patient leaving ED prior to physicioan assesment, direct admission to geriatric hospital ie bypassing ED, missing hospital records, missing personal identification number, insufficient documentation to determine outcome sepsis	prospective	538; 78Y; 42%
Wiwatcharagoses 2016	severe sepsis	PCT	adults	sepsis-2	ED; Thailand	patients of at least 20Y old, presenting tot the ED with symptoms of systemic infection	antibiotics before blood culture, involved in any accidents, organ transplant, autoimmunity or malignancy, immunosuppressive drugs, returned laboratory findings such as contaminated pathogens, viral or fungal infection	prospective	110; 51.7Y mean; 31%
	septic shock								110; 51.7Y; 12%
	Bacteraemia								110; 51.7Y; 21%
Woo 2021	Sepsis, ns	MDW, CRP, PCT, WBC, MDW+CRP, MDW+CRP, MDW+PCT	adults	sepsis-3	ED; Korea	Age 18-80 years, ED visit, physician ordered a complete blood count with differential tests	pregnancy, enrolled during previous visit, invalid laboratory results	prospective	549; 59.2Y; 34%
Wyllie 2004	Bacteraemia	WBC, lymphocyt#, neutrophil#	adults	positive bloodculture	ED; UK	Adult, admission as emergency to general medical or infectious diseases services	Admission to haematology or cardiology, no full blood count on admission, lymphocyte count > 10 x 10^9/l, Neutrophil count > 75 x 10^9/l	prospective	7182; 64.6Y; 74%
Wyllie 2005	Bacteraemia	CRP	adults	positive bloodculture	ED; UK	Adult, admission as emergency to general medical or infectious diseases services, blood culture	Admission to haematology or cardiology, no full blood count on admission, lymphocyte count > 10 x 10^9/l, Neutrophil count > 75 x 10^9/l, no blood cultures	prospective	4145; 64.5Y; 7.8%
Yu 2022	Sepsis, ns	IL-6, BUN, IL6+BUN	adults	sepsis-3	ED; China	critically ill	Pregnancy; patients with malignant tumors, hematological diseases, connective tissue diseases or receiving immunosup- pressive therapy.	prospective	128; 72Y; 49%
Ding 2022	Pneumonia	CRP	adults	chest CT	ED; China	Adult, presenting to the ED with respiratory symptoms and	Pregnancy, no CT-scan	prospective	727; 43.5Y; 31%
Flanders 2004	Pneumonia	CRP	adults	chest radiograph	ED + acute care	Adult, presenting with acute cough	Pregnancy, systemic inflammatory disorders, coexistent infections, severe tissue damage in	prospective	168; 39Y; 12%
Groeneveld 2019	Pneumonia	CRP, PCT, MR-	adults	chest radiograph	GP; Netherlands	Adult, referred for chest radiography by their GP. Complaints	None	prospective	249; 56Y; 12%
Haran 2013	Pneumonia	GM-CSF, IFN-Gamma,	adults	chest radiograph	ED; US	Adult patients presenting to the ED with fever and a cough	Symptoms >5 days, history of liver disease, immunorepressant medications, prior diagnosis of	prospective	80; 35.1Y; 18%
Heining 2016	Pneumonia	PCT	adults	chest radiograph	ED; Germany	Acute dyspnea in ED	None	prospective	172; 70.7Y; 17%
Holm 2007a	Pneumonia	CRP, WBC	adults	chest radiograph	GP; Denmark	Age ≥18 years, a GP's diagnosis of lower respiratory tract	Hospitalisation in the preceding 7 days, severity of illness requiring hospitalisation, pregnancy,	prospective	364; 50Y; 13%
Holm 2007b	Pneumonia	PCT	adults	chest radiograph	GP; Denmark	Age ≥18 years, a GP's diagnosis of lower respiratory tract	Hospitalisation in the preceding 7 days, severity of illness requiring hospitalisation, pregnancy,	prospective	364; unknown; 13%
Hopstaken 2003	Pneumonia	CRP, ESR	adults	chest radiograph	GP; Netherlands	Age ≥18 years & new (i.e. less than 29 days) or increasing	Pregnancy and lactation; history of hypersensitivity to penicillin or macrolide antibiotics,	cross-	246; 52Y; 13%
Hopstaken 2009	Pneumonia	CRP, Fibrinogen, LBP	adults	chest radiograph	GP; Netherlands	Age ≥18 years & new (i.e. less than 29 days) or increasing	Pregnancy and lactation; history of hypersensitivity to penicillin or macrolide antibiotics,	prospective	95; 52.4Y; 12%
LeBel 2015	Pneumonia	CRP, CRP+PCT, PCT	adults	Adjudication committee	ED; France	Age >18 years , suspection of CAP by physician of ED	Pregnancy, patients in palliative care or with anticipated barriers to completing follow-up data	prospective	200; 63.9Y; 49%
Loubet 2020	Pneumonia	CRP, PCT, WBC	adults	Adjudication committee	ED; France	Age >18y, new onset of systemic features (sweat, fever, chills,	None	prospective	319; 68Y; 51%
Maisel 2012	Pneumonia	PCT	adults	Adjudication committee	ED; international	Adult patients presenting to the ED with a chief complaint of	<18Y, unable to provide consent, acute ST-elevation myocardial infarction, hemodialysis or	prospective	1641; 63.5Y; 9%
Melbye 1988	Pneumonia	CRP, ESR, lymphocyt	adults	chest radiograph	GP + ED; Norway	Adult patients treated with antibiotics by GP for suspected	Admission to hospital, too ill to attend outpatient clinic 1-4 days after the start of antibiotic	prospective	71; 48Y; 15%
Melbye 1992	Pneumonia	CRP, ESR, WBC	adults	chest radiograph	ED; Norway	Adults presenting with symptoms of respiratory or throat	Severe dyspnoea in need of urgent treatment, pregnancy	prospective	402; 33.2Y; 5%
Moberg 2016	Pneumonia	CRP, WBC	adults	chest radiograph	GP; Sweden	Adults with suspected pneumonia, symptoms > 24h	Pregnancy, COPD, living in nursing home, antibiotic treatment for LRTI within 2 weeks before	prospective	100; 56Y; 45%
Mueller 2007	Pneumonia	CRP, PCT, WBC	adults	chest radiograph	ED; Switzerland	Adults presenting with suspected LRTI as principal diagnosis	Cystic fibrosis, active pulmonary tuberculosis, HAP and severely immunocompromised	prospective	545; 67.1Y; 68%
Ruiz-Gonzalez 2016	Pneumonia	CRP	adults	chest radiograph	ED; Spain	Adults, respiratory symptoms with or without fever, disease	Final diagnosis of acute heart failure, pulmonary embolism, lung cancer, URTI, severe	prospective	923; 74.8Y; 60%
Steurer 2011	Pneumonia	CRP	adults	BTS Guidelines for the	GP; Switzerland	Age ≥18 years, new or worsened (>24h) cough and subjective	Chronic lung disease (except chronic bronchitis), hospital-acquired cough and fever, HIV	prospective	621; 46.8Y; 20%
Teepe 2017	Pneumonia	CRP	adults	chest radiograph	GP; Europe	Age ≥18 years, first presentation with main symptom of acute	Pregnancy, lactation, treatment with antibiotics in the previous month, immunodeficiency	prospective	3104; 50Y; 0.3%
VanVugt 2013	Pneumonia	CRP, PCT	adults	chest radiograph	GP; Europe	Adult, acute cough	No chest radiograph or of insufficient quality	prospective	2820; 50Y; 5%
Wussler 2019	Pneumonia	CRP, IL-6, PCT	adults	Adjudication committee	ED; Switzerland	Adult patients presenting with acute dyspnea	Hemodialysis, no measurement of PCT, IL-6, CRP available	prospective	690; 74Y; 26%

Figure 3: Pneumonia: Forest plot for CRP by cut-off value

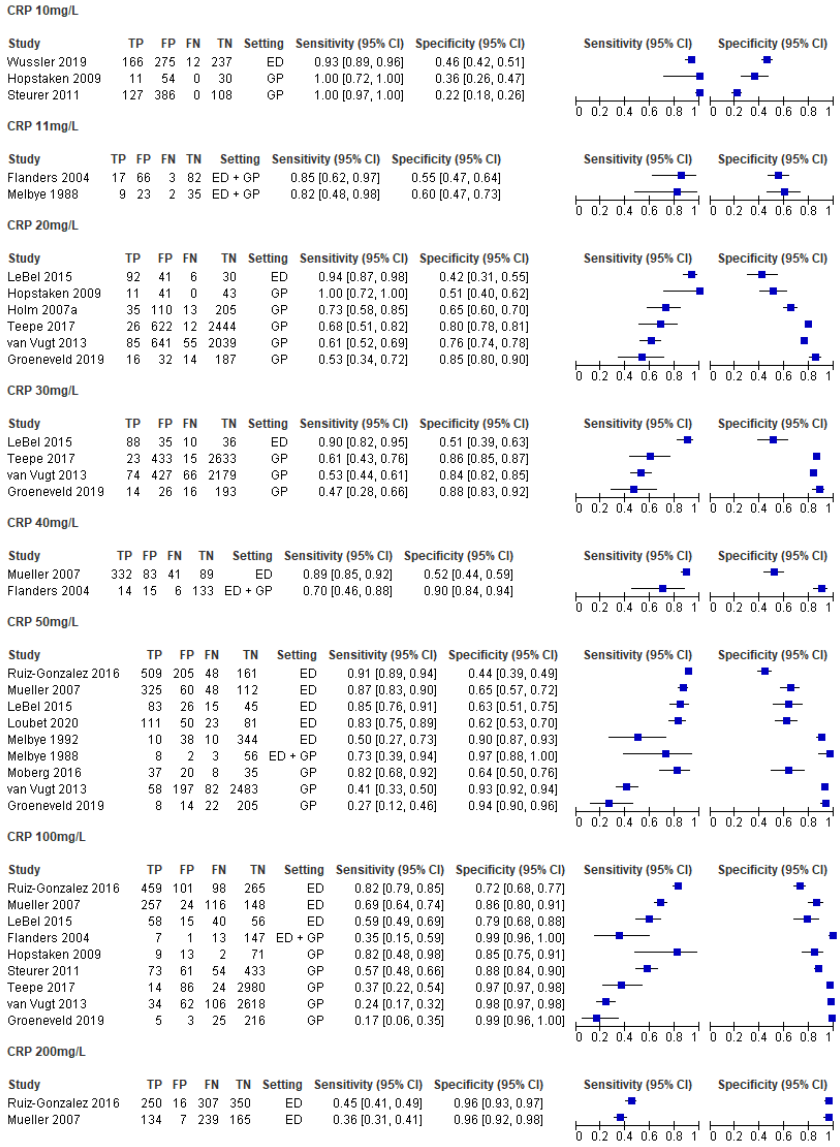


Figure 5: Pneumonia: Forest plot for PCT by cut-off value

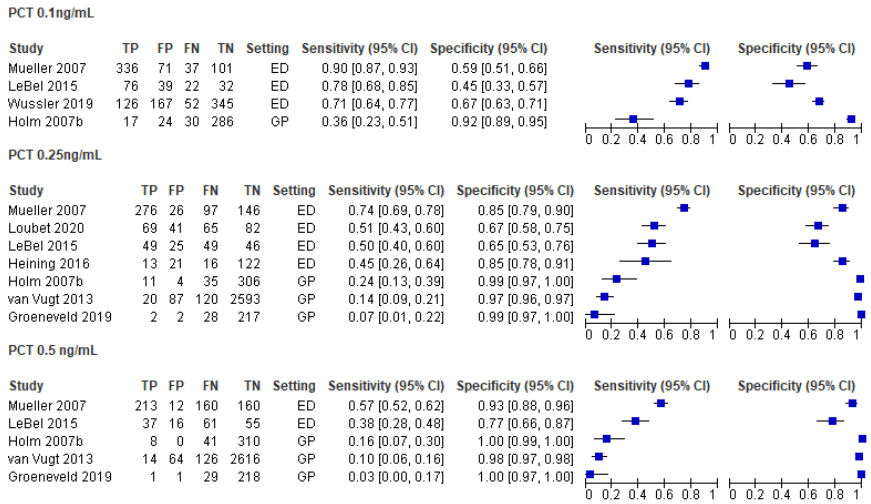
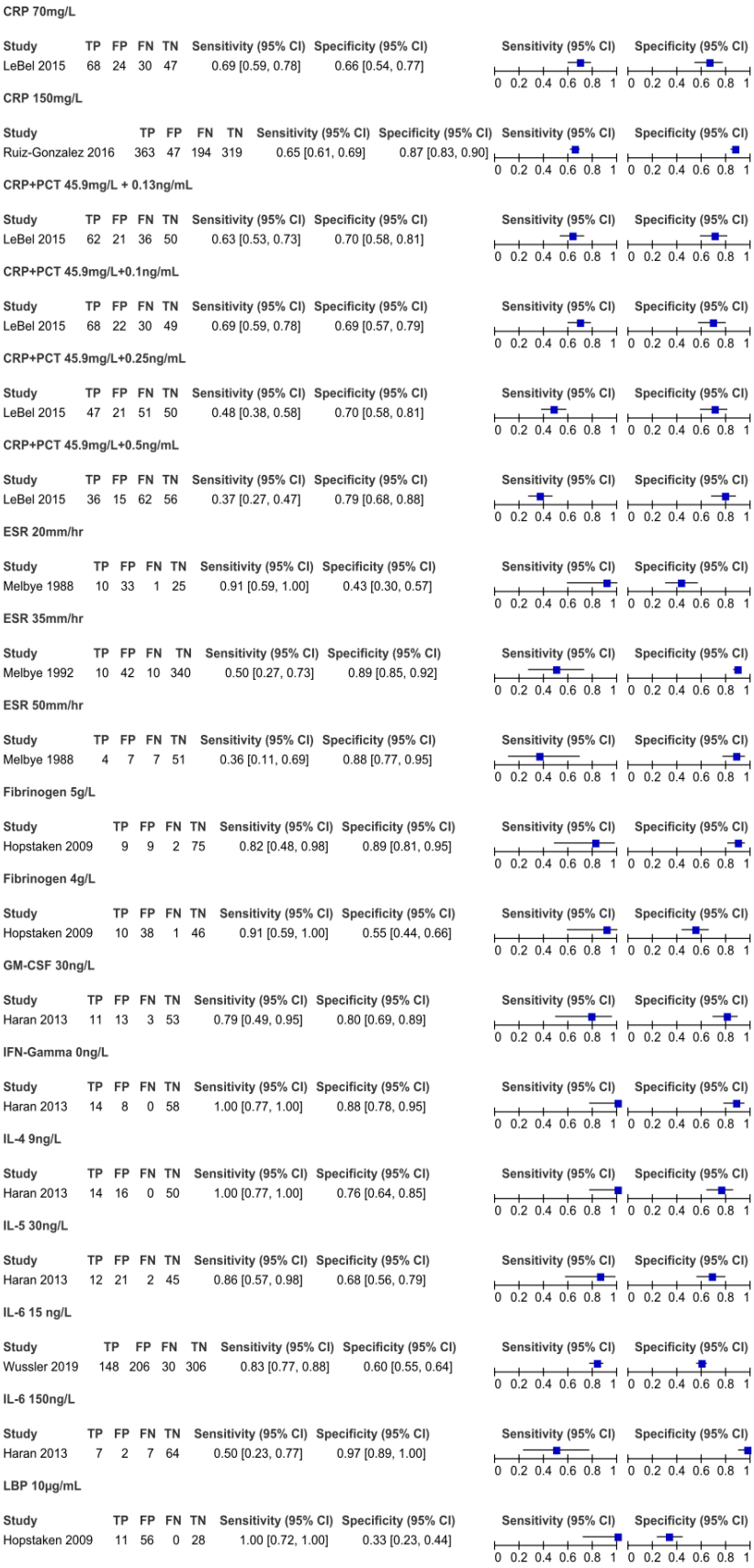
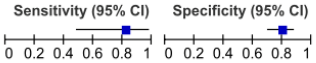


Figure 7: Pneumonia: Forest plot for other biomarkers by cut-off value



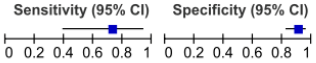
LBP 20µg/mL

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hopstaken 2009	9	17	2	67	0.82 [0.48, 0.98]	0.80 [0.70, 0.88]



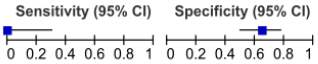
LBP 30µg/mL

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hopstaken 2009	8	8	3	76	0.73 [0.39, 0.94]	0.90 [0.82, 0.96]



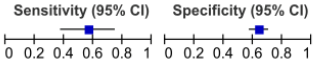
lymphocyt% 50%

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Melbye 1988	0	17	10	31	0.00 [0.00, 0.31]	0.65 [0.49, 0.78]



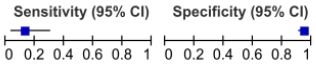
MR-PROADM 0.646per 10mg/L increase

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Groeneveld 2019	17	79	13	140	0.57 [0.37, 0.75]	0.64 [0.57, 0.70]



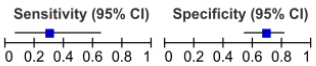
MR-PROADM 1per 10mg/L increase

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Groeneveld 2019	4	12	26	207	0.13 [0.04, 0.31]	0.95 [0.91, 0.97]



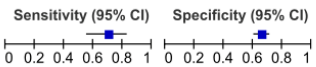
neutrophil% 65%

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Melbye 1988	3	15	7	33	0.30 [0.07, 0.65]	0.69 [0.54, 0.81]



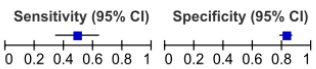
PCT 0.06ng/mL

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Holm 2007b	33	106	14	204	0.70 [0.55, 0.83]	0.66 [0.60, 0.71]



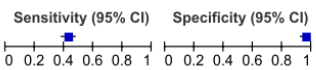
PCT 0.08ng/mL

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Holm 2007b	23	54	24	256	0.49 [0.34, 0.64]	0.83 [0.78, 0.87]



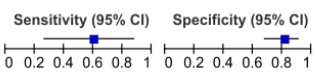
PCT 1 ng/mL

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Mueller 2007	160	7	213	165	0.43 [0.38, 0.48]	0.96 [0.92, 0.98]



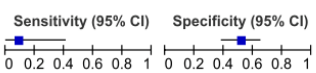
stabs% 10%

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Melbye 1988	6	9	4	39	0.60 [0.26, 0.88]	0.81 [0.67, 0.91]



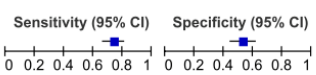
WBC <6500 cells/mcrL

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Melbye 1988	1	28	10	30	0.09 [0.00, 0.41]	0.52 [0.38, 0.65]



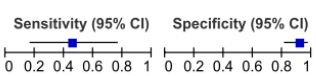
WBC 7000cells/µL

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Loubet 2020	105	61	37	69	0.74 [0.66, 0.81]	0.53 [0.44, 0.62]



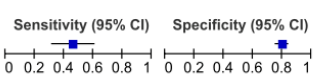
WBC 9500 cell/mcrL

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Melbye 1988	5	5	6	53	0.45 [0.17, 0.77]	0.91 [0.81, 0.97]



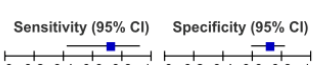
WBC 10000cells/µL

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Holm 2007a	22	64	26	250	0.46 [0.31, 0.61]	0.80 [0.75, 0.84]



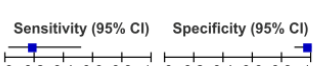
WBC 10500 cells/µL

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Haran 2013	10	19	4	47	0.71 [0.42, 0.92]	0.71 [0.59, 0.82]



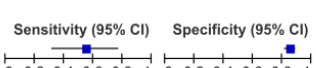
WBC 11500 cells/mcrL

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Melbye 1988	2	2	9	56	0.18 [0.02, 0.52]	0.97 [0.88, 1.00]



WBC 10400 cells/mcrL

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Melbye 1992	11	57	9	325	0.55 [0.32, 0.77]	0.85 [0.81, 0.88]



WBC 15000 cells/mcrL

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Moberg 2016	7	5	38	50	0.16 [0.06, 0.29]	0.91 [0.80, 0.97]

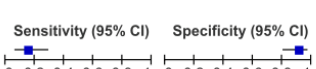
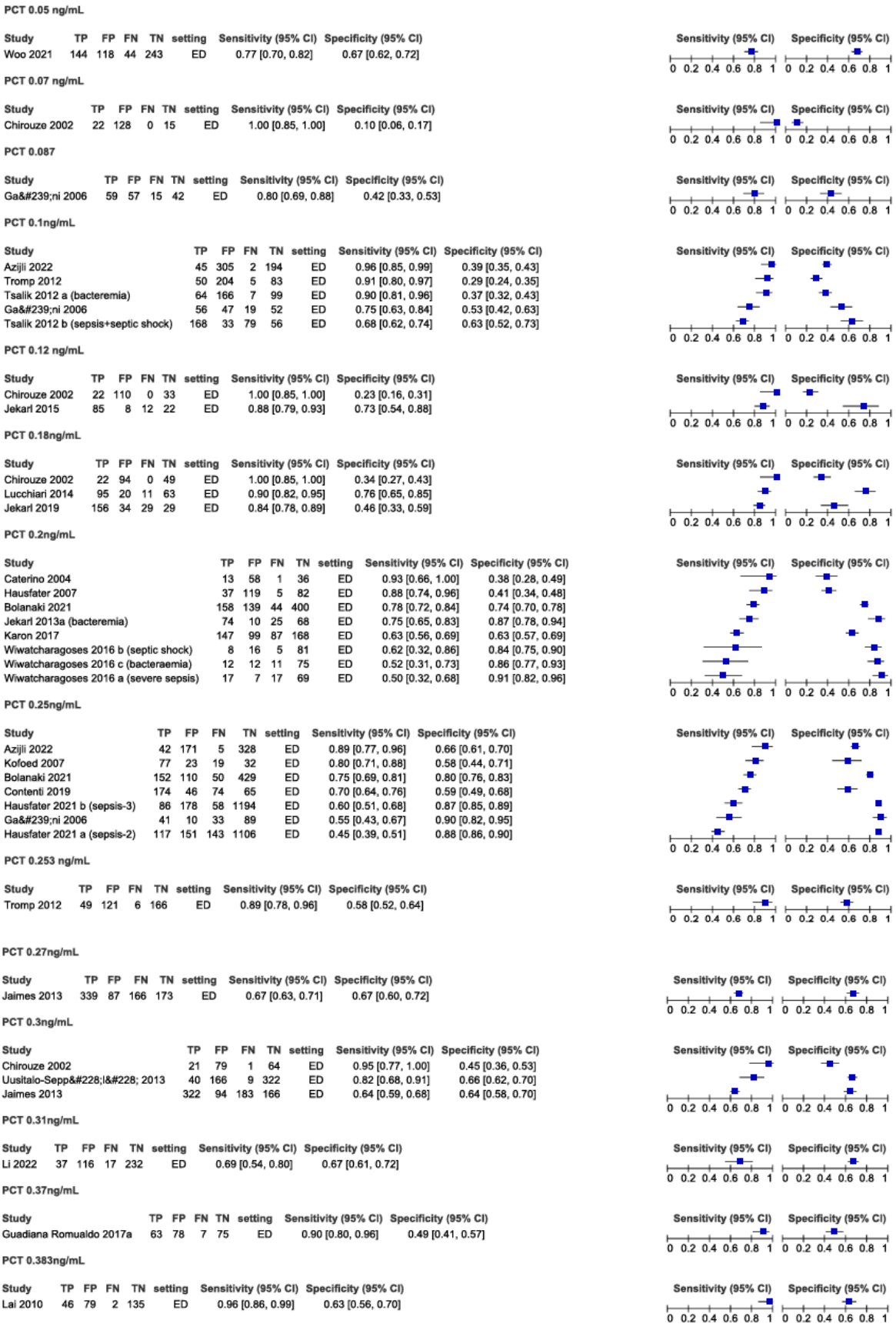
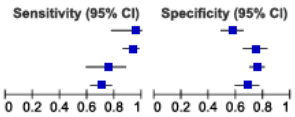


Figure 11: Sepsis: Forest plot for PCT by cut-off value



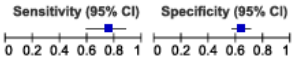
PCT 0.4 ng/mL

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Chirouze 2002	21	61	1	82	ED	0.95 [0.77, 1.00]	0.57 [0.49, 0.66]
Jekarl 2013b (severe sepsis/septic shock)	73	25	5	74	ED	0.94 [0.86, 0.98]	0.75 [0.65, 0.83]
Tudela 2010	28	58	9	180	ED	0.76 [0.59, 0.88]	0.76 [0.70, 0.81]
Ruangsomboon 2020 a (sepsis or septic shock)	98	35	41	76	ED	0.71 [0.62, 0.78]	0.68 [0.59, 0.77]



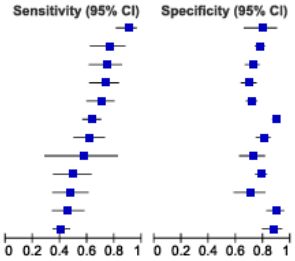
PCT 0.45 ng/ml

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Romualdo 2014	28	68	9	121	ED	0.76 [0.59, 0.88]	0.64 [0.57, 0.71]



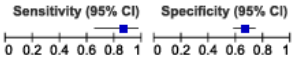
PCT 0.5 ng/mL

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Ahmadinejad 2009	64	10	7	39	ED	0.90 [0.81, 0.96]	0.80 [0.66, 0.90]
Azijli 2022	36	112	11	387	ED	0.77 [0.62, 0.88]	0.78 [0.74, 0.81]
Tromp 2012	41	80	14	207	ED	0.75 [0.61, 0.85]	0.72 [0.67, 0.77]
Tsalik 2012 a (bacteremia)	52	81	19	184	ED	0.73 [0.61, 0.83]	0.69 [0.64, 0.75]
Su 2011	59	135	25	339	ED	0.70 [0.59, 0.80]	0.72 [0.67, 0.76]
Bolanaki 2021	128	58	74	481	ED	0.63 [0.56, 0.70]	0.89 [0.86, 0.92]
Ognibene 2022	47	46	29	186	ED	0.62 [0.50, 0.73]	0.80 [0.74, 0.85]
Caterino 2004	8	26	6	68	ED	0.57 [0.29, 0.82]	0.72 [0.62, 0.81]
Li 2022	26	75	27	275	ED	0.49 [0.35, 0.63]	0.79 [0.74, 0.83]
Visveswari 2019	29	19	32	46	ED	0.48 [0.35, 0.61]	0.71 [0.58, 0.81]
Gaïni 2006	34	10	40	89	ED	0.46 [0.34, 0.58]	0.90 [0.82, 0.95]
Tsalik 2012 b (sepsis+septic shock)	101	11	146	78	ED	0.41 [0.35, 0.47]	0.88 [0.79, 0.94]



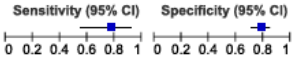
PCT 0.55 ng/mL

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Chirouze 2002	19	48	3	95	ED	0.86 [0.65, 0.97]	0.66 [0.58, 0.74]



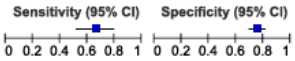
PCT 0.9 ng/mL

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Chirouze 2002	17	31	5	112	ED	0.77 [0.55, 0.92]	0.78 [0.71, 0.85]



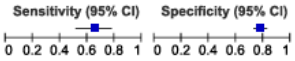
PCT 0.94 ng/mL

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Ruangsomboon 2020 b (septic shock)	32	49	16	153	ED	0.67 [0.52, 0.80]	0.76 [0.69, 0.81]



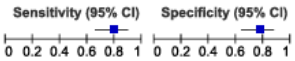
PCT 1 ng/mL

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Tromp 2012	36	63	19	224	ED	0.65 [0.51, 0.78]	0.78 [0.73, 0.83]



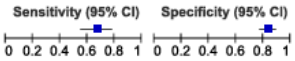
PCT 1.3 ng/mL

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Guadiana Romualdo 2018	39	12	10	41	ED	0.80 [0.66, 0.90]	0.77 [0.64, 0.88]



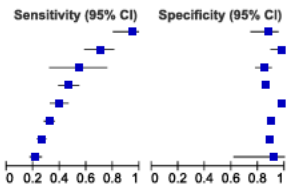
PCT 1.56ng/mL

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Guadiana Romualdo 2017a	47	25	23	128	ED	0.67 [0.55, 0.78]	0.84 [0.77, 0.89]



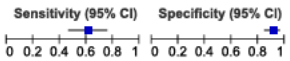
PCT 2ng/mL

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Oh 2009	31	6	2	41	ED	0.94 [0.80, 0.99]	0.87 [0.74, 0.95]
Ahmadinejad 2009	50	1	21	48	ED	0.70 [0.58, 0.81]	0.98 [0.89, 1.00]
Chirouze 2002	12	22	10	121	ED	0.55 [0.32, 0.76]	0.85 [0.78, 0.90]
Ljungström 2017 c (severe sepsis/shock | sepsis-2)	79	203	90	1200	ED	0.47 [0.39, 0.55]	0.86 [0.84, 0.87]
Bolanaki 2021	80	16	122	523	ED	0.40 [0.33, 0.47]	0.97 [0.95, 0.98]
Ljungström 2017 b (sepsis | sepsis-3)	180	106	380	906	ED	0.32 [0.28, 0.36]	0.90 [0.87, 0.91]
Ljungström 2017 a (sepsis | sepsis-2)	176	103	491	802	ED	0.26 [0.23, 0.30]	0.89 [0.86, 0.91]
Loots 2022	71	1	253	11	GP	0.22 [0.18, 0.27]	0.92 [0.62, 1.00]



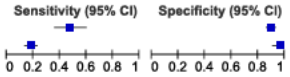
PCT 2.02ng/mL

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Guadiana Romualdo 2017b	29	9	18	96	ED	0.62 [0.46, 0.75]	0.91 [0.84, 0.96]



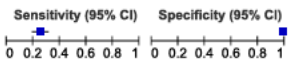
PCT 3 ng/mL

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Tsalik 2012 a (bacteremia)	34	27	37	238	ED	0.48 [0.36, 0.60]	0.90 [0.86, 0.93]
Tsalik 2012 b (sepsis+septic shock)	45	3	202	86	ED	0.18 [0.14, 0.24]	0.97 [0.90, 0.99]



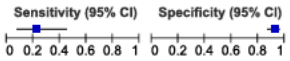
PCT 5ng/mL

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Bolanaki 2021	51	6	151	533	ED	0.25 [0.19, 0.32]	0.99 [0.98, 1.00]



PCT 6.2 ng/mL

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Chirouze 2002	5	11	17	132	ED	0.23 [0.08, 0.45]	0.92 [0.87, 0.96]



PCT 10ng/mL

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Ljungström 2017 c (severe sepsis/shock | sepsis-2)	45	63	124	1340	ED	0.27 [0.20, 0.34]	0.96 [0.94, 0.97]
Ahmadinejad 2009	18	0	53	49	ED	0.25 [0.16, 0.37]	1.00 [0.93, 1.00]
Bolanaki 2021	33	2	169	537	ED	0.16 [0.12, 0.22]	1.00 [0.99, 1.00]
Ljungström 2017 b (sepsis | sepsis-3)	86	26	474	986	ED	0.15 [0.12, 0.19]	0.97 [0.96, 0.98]
Ljungström 2017 a (sepsis | sepsis-2)	73	33	594	872	ED	0.11 [0.09, 0.14]	0.96 [0.95, 0.97]

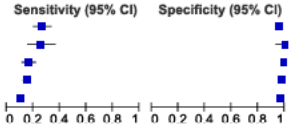
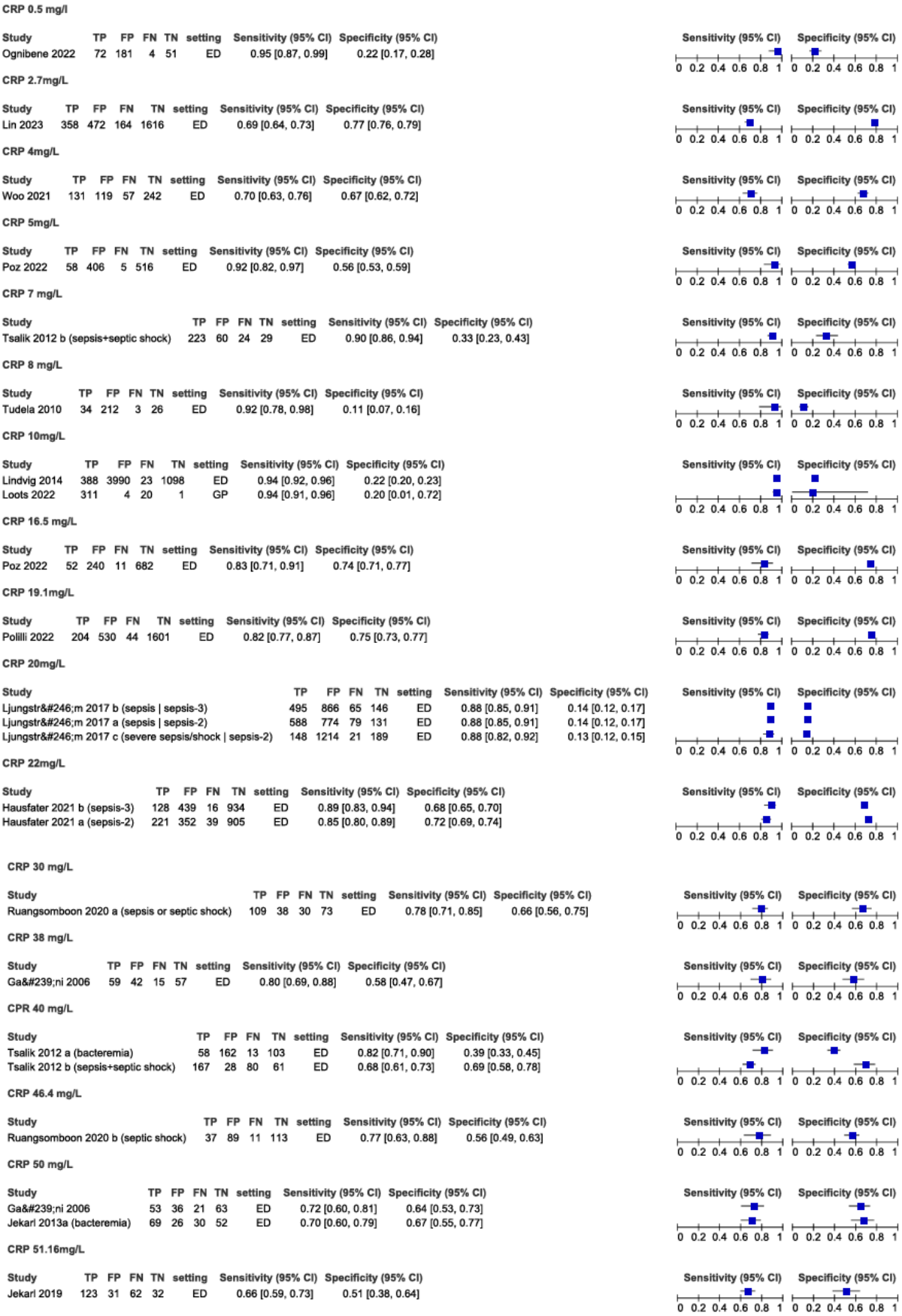


Figure 13: Sepsis: Forest plot for CRP



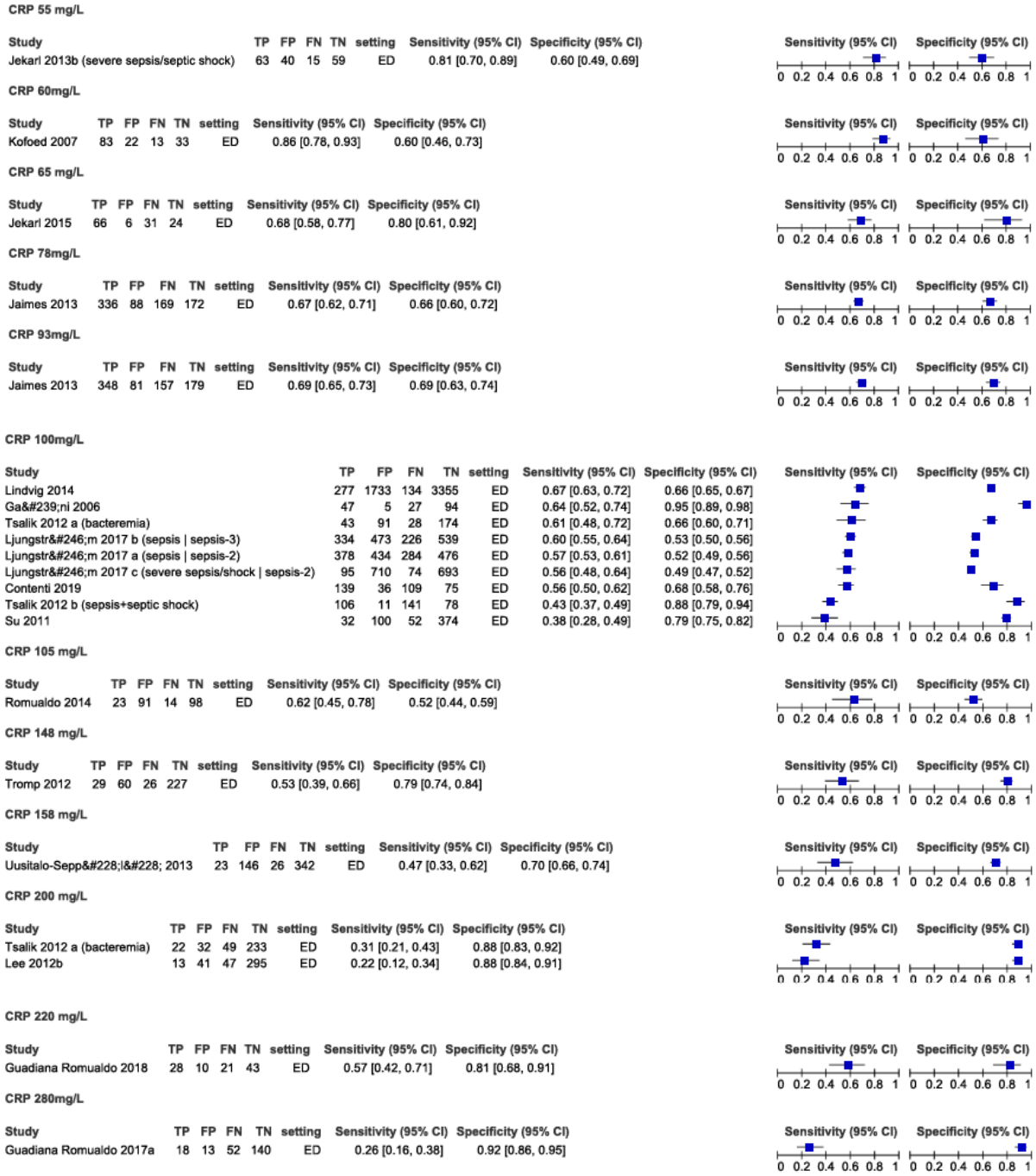
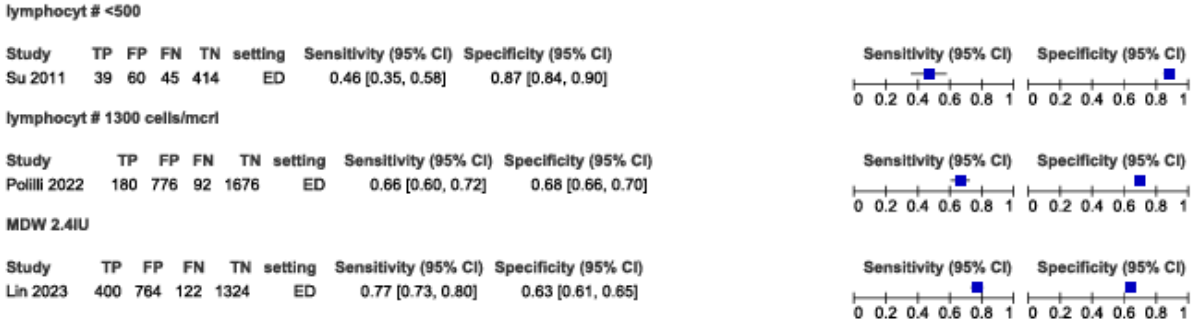
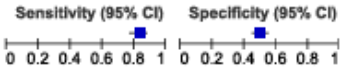


Figure 15: Sepsis: Forest plot for WBC



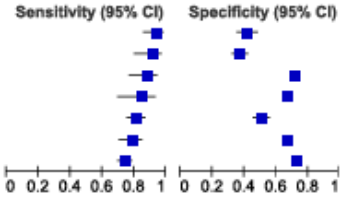
MDW 19.8

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Woo 2021	156	181	32	180	ED	0.83 [0.77, 0.88]	0.50 [0.45, 0.55]



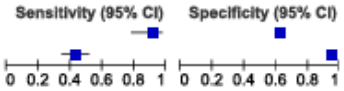
MDW 20IU

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Ognibene 2022	71	135	5	97	ED	0.93 [0.85, 0.98]	0.42 [0.35, 0.48]
Li 2022	49	219	5	129	ED	0.91 [0.80, 0.97]	0.37 [0.32, 0.42]
Poz 2022	55	261	8	661	ED	0.87 [0.77, 0.94]	0.72 [0.69, 0.75]
Malinovska 2022 b (septic shock)	36	2681	7	5228	ED	0.84 [0.69, 0.93]	0.66 [0.65, 0.67]
Woo 2021	153	178	35	183	ED	0.81 [0.75, 0.87]	0.51 [0.45, 0.56]
Malinovska 2022 a (sepsis)	107	2595	30	5220	ED	0.78 [0.70, 0.85]	0.67 [0.66, 0.68]
Crouser 2020	285	496	100	1277	ED	0.74 [0.69, 0.78]	0.72 [0.70, 0.74]



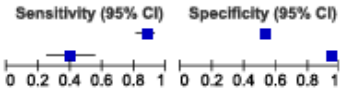
MDW 20U and NLR 10

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Malinovska 2022 b (septic shock)	39	2990	4	4919	ED	0.91 [0.78, 0.97]	0.62 [0.61, 0.63]
Malinovska 2022 a (sepsis)	59	422	78	7393	ED	0.43 [0.35, 0.52]	0.95 [0.94, 0.95]



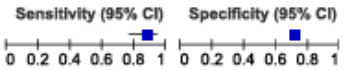
MDW 20U or NLR 10

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Malinovska 2022 a (sepsis)	120	3673	17	4142	ED	0.88 [0.81, 0.93]	0.53 [0.52, 0.54]
Malinovska 2022 b (septic shock)	17	482	26	7427	ED	0.40 [0.25, 0.56]	0.94 [0.93, 0.94]



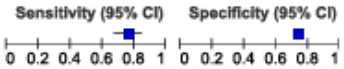
MDW 20.1

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Poz 2022	55	261	8	661	ED	0.87 [0.77, 0.94]	0.72 [0.69, 0.75]



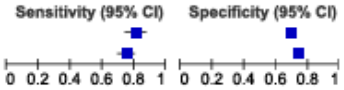
MDW 20.5IU

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Crouser 2017	75	330	23	892	ED	0.77 [0.67, 0.85]	0.73 [0.70, 0.75]



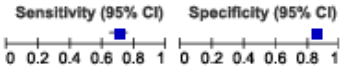
MDW 21.5UI

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Hausfater 2021 b (sepsis-3)	117	426	27	947	ED	0.81 [0.74, 0.87]	0.69 [0.66, 0.71]
Hausfater 2021 a (sepsis-2)	195	339	65	918	ED	0.75 [0.69, 0.80]	0.73 [0.70, 0.75]



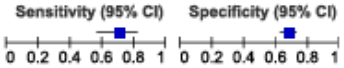
MDW 22

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Polilli 2022	191	357	81	2095	ED	0.70 [0.64, 0.76]	0.85 [0.84, 0.87]



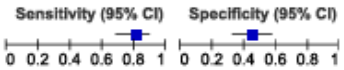
MDW 23.41UI

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Li 2022	38	113	16	235	ED	0.70 [0.56, 0.82]	0.68 [0.62, 0.72]



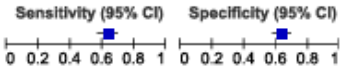
neutrophil% 40-75

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Visveswari 2019	49	36	12	29	ED	0.80 [0.68, 0.89]	0.45 [0.32, 0.57]



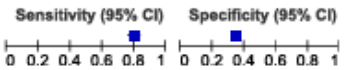
Neutrophil % 79%

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Karon 2017	148	98	86	169	ED	0.63 [0.57, 0.69]	0.63 [0.57, 0.69]



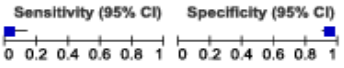
Neutrophil # ≥7.0 × 109 /L or ≤ 2.0cells/µL

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Lindvig 2014	334	3319	84	1762	ED	0.80 [0.76, 0.84]	0.35 [0.33, 0.36]



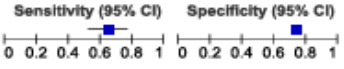
neutrophil # 1000 cells/mcrL

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Tudela 2010	1	15	36	223	ED	0.03 [0.00, 0.14]	0.94 [0.90, 0.96]



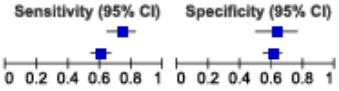
neutrophil # 7220 cells/mcrL

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Poz 2022	41	245	22	677	ED	0.65 [0.52, 0.77]	0.73 [0.70, 0.76]



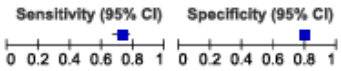
Neutrophil # 7500cells/µL

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Kofoed 2007	71	20	25	35	ED	0.74 [0.64, 0.82]	0.64 [0.50, 0.76]
Karon 2017	142	105	92	162	ED	0.61 [0.54, 0.67]	0.61 [0.55, 0.67]



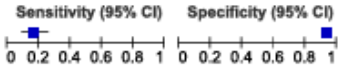
neutrophil # 8900 cells/mcrl

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Polilli 2022	197	514	75	1938	ED	0.72 [0.67, 0.78]	0.79 [0.77, 0.81]



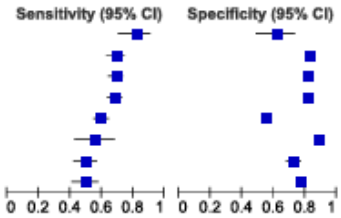
WBC <4000

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Su 2011	14	32	70	442	ED	0.17 [0.09, 0.26]	0.93 [0.91, 0.95]



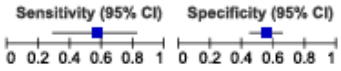
WBC <4000 or >12000 cells/µL

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Visveswari 2019	50	25	11	40	ED	0.82 [0.70, 0.91]	0.62 [0.49, 0.73]
Hausfater 2021 a (sepsis-2)	179	214	81	1043	ED	0.69 [0.63, 0.74]	0.83 [0.81, 0.85]
Crouser 2020	265	325	120	1447	ED	0.69 [0.64, 0.73]	0.82 [0.80, 0.83]
Crouser 2019	262	325	123	1448	ED	0.68 [0.63, 0.73]	0.82 [0.80, 0.83]
Lindvig 2014	249	2285	169	2796	ED	0.60 [0.55, 0.64]	0.55 [0.54, 0.56]
Poz 2022	35	109	28	813	ED	0.56 [0.42, 0.68]	0.88 [0.86, 0.90]
Woo 2021	93	99	95	262	ED	0.49 [0.42, 0.57]	0.73 [0.68, 0.77]
Hausfater 2021 b (sepsis-3)	71	316	73	1056	ED	0.49 [0.41, 0.58]	0.77 [0.75, 0.79]



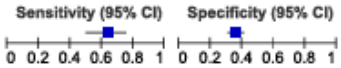
WBC <4300 or > 11400 cells/µL

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Caterino 2004	8	42	6	52	ED	0.57 [0.29, 0.82]	0.55 [0.45, 0.66]



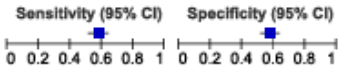
WBC >9.000 cells/µL

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Lee 2012b	38	215	22	121	ED	0.63 [0.50, 0.75]	0.36 [0.31, 0.41]



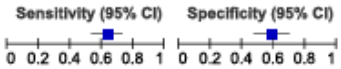
WBC 9700 cells/µL

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Karon 2017	135	113	99	154	ED	0.58 [0.51, 0.64]	0.58 [0.52, 0.64]



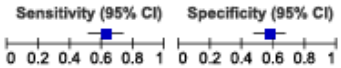
WBC 10.000 cells/µL

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Jekarl 2013a (bacteremia)	63	32	36	46	ED	0.64 [0.53, 0.73]	0.59 [0.47, 0.70]



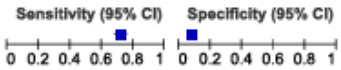
WBC 11.000 cells/µL

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Jekarl 2013b (severe sepsis/septic shock)	49	42	29	57	ED	0.63 [0.51, 0.74]	0.58 [0.47, 0.67]



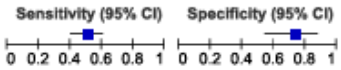
WBC 11100cells/µL

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Lin 2023	376	1923	146	165	ED	0.72 [0.68, 0.76]	0.08 [0.07, 0.09]



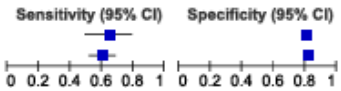
WBC 11.500 cells/µL

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Jekarl 2015	49	8	48	22	ED	0.51 [0.40, 0.61]	0.73 [0.54, 0.88]



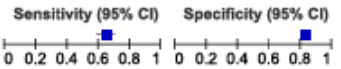
WBC 12000cells/µL

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Malinovska 2022 b (septic shock)	28	1534	15	6375	ED	0.65 [0.49, 0.79]	0.81 [0.80, 0.81]
Malinovska 2022 a (sepsis)	83	1461	54	6354	ED	0.61 [0.52, 0.69]	0.81 [0.80, 0.82]



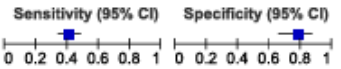
WBC 12200 cells/mcrl

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Polilli 2022	175	427	97	2025	ED	0.64 [0.58, 0.70]	0.83 [0.81, 0.84]



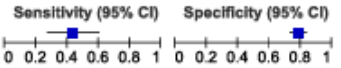
WBC 13660cells/µl

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Jekarl 2019	76	14	109	49	ED	0.41 [0.34, 0.49]	0.78 [0.66, 0.87]



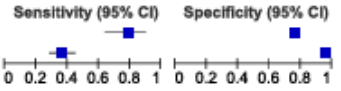
WBC 15000 cells/mcrL

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Tudela 2010	16	51	21	187	ED	0.43 [0.27, 0.61]	0.79 [0.73, 0.84]



WBC >12000 or <4000 and NLR 10

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Malinovska 2022 b (septic shock)	34	1930	9	5979	ED	0.79 [0.64, 0.90]	0.76 [0.75, 0.77]
Malinovska 2022 a (sepsis)	50	336	87	7479	ED	0.36 [0.28, 0.45]	0.96 [0.95, 0.96]



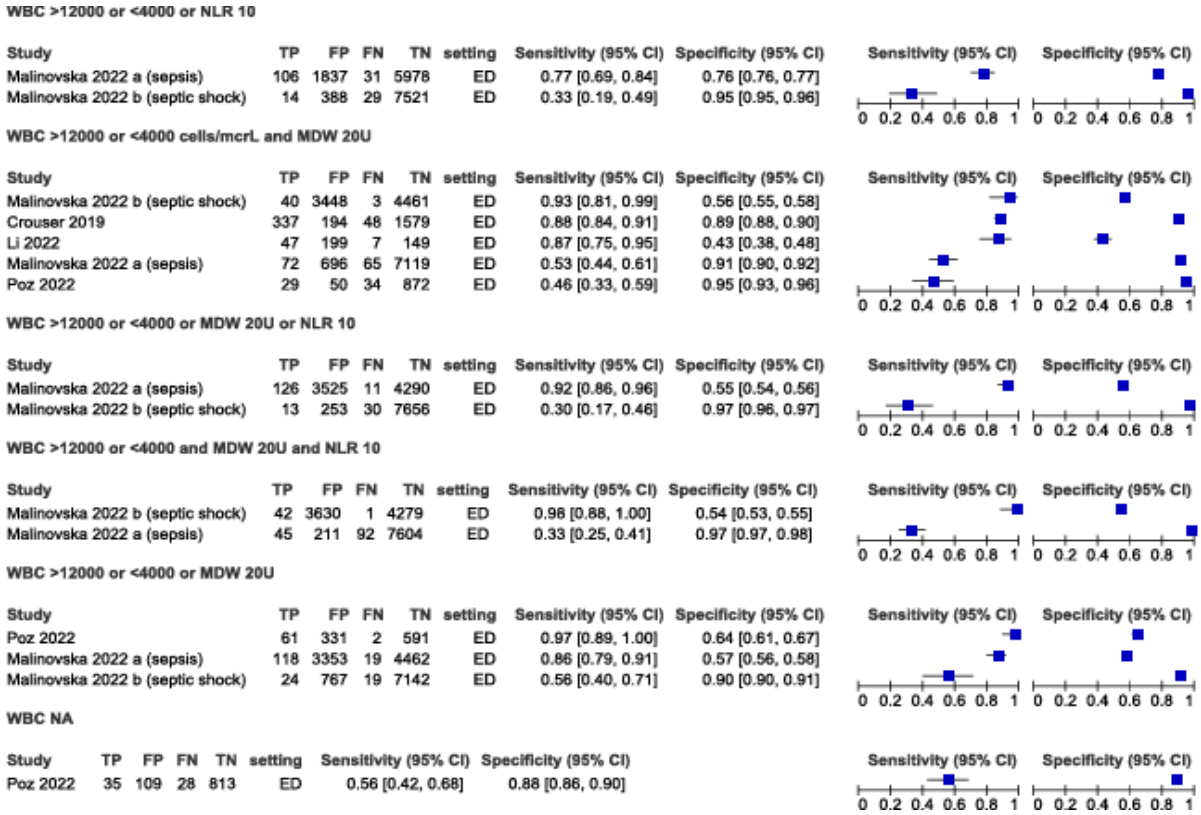


Figure 18: Sepsis: Forest plot for lactate

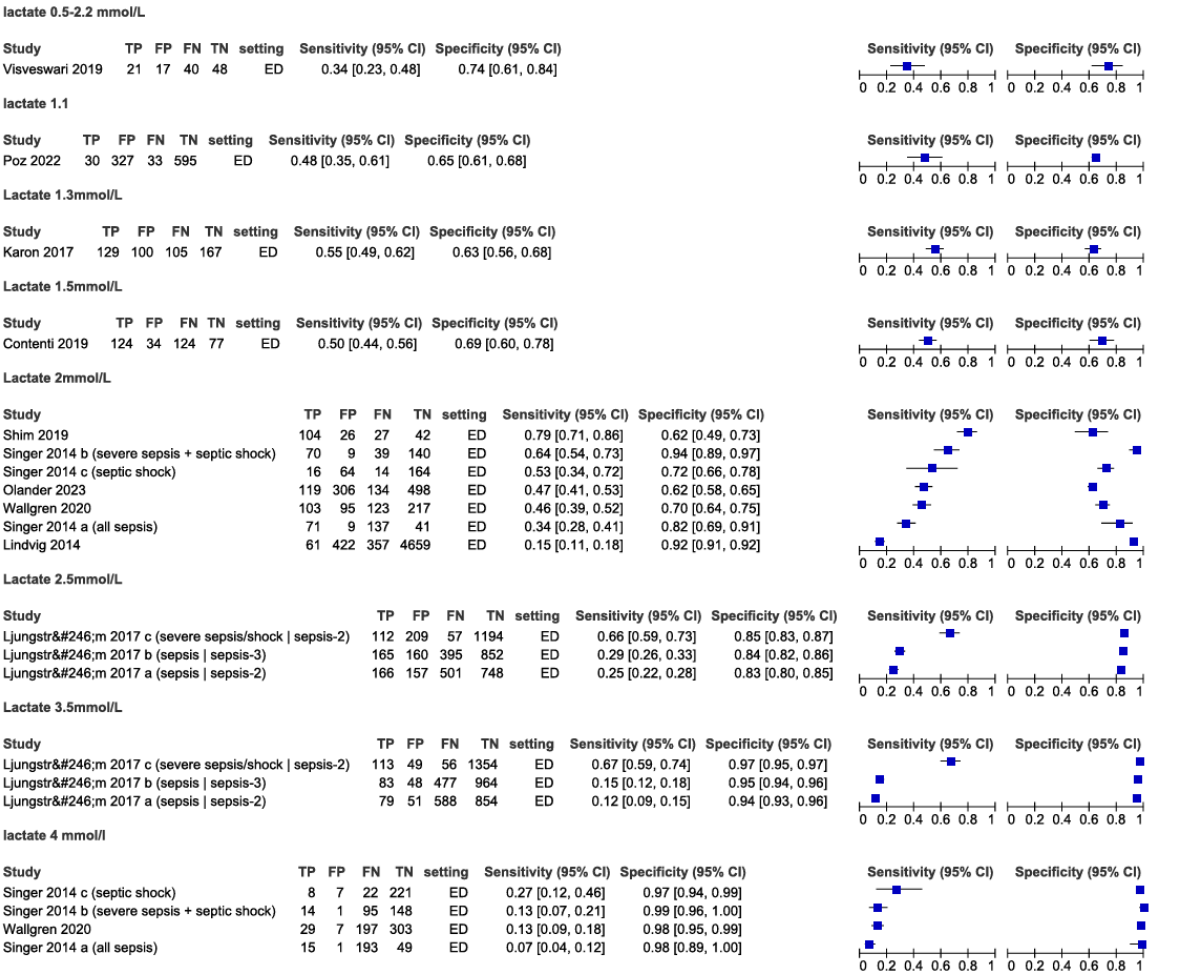


Figure 20: Sepsis: Forest plot for presepsin

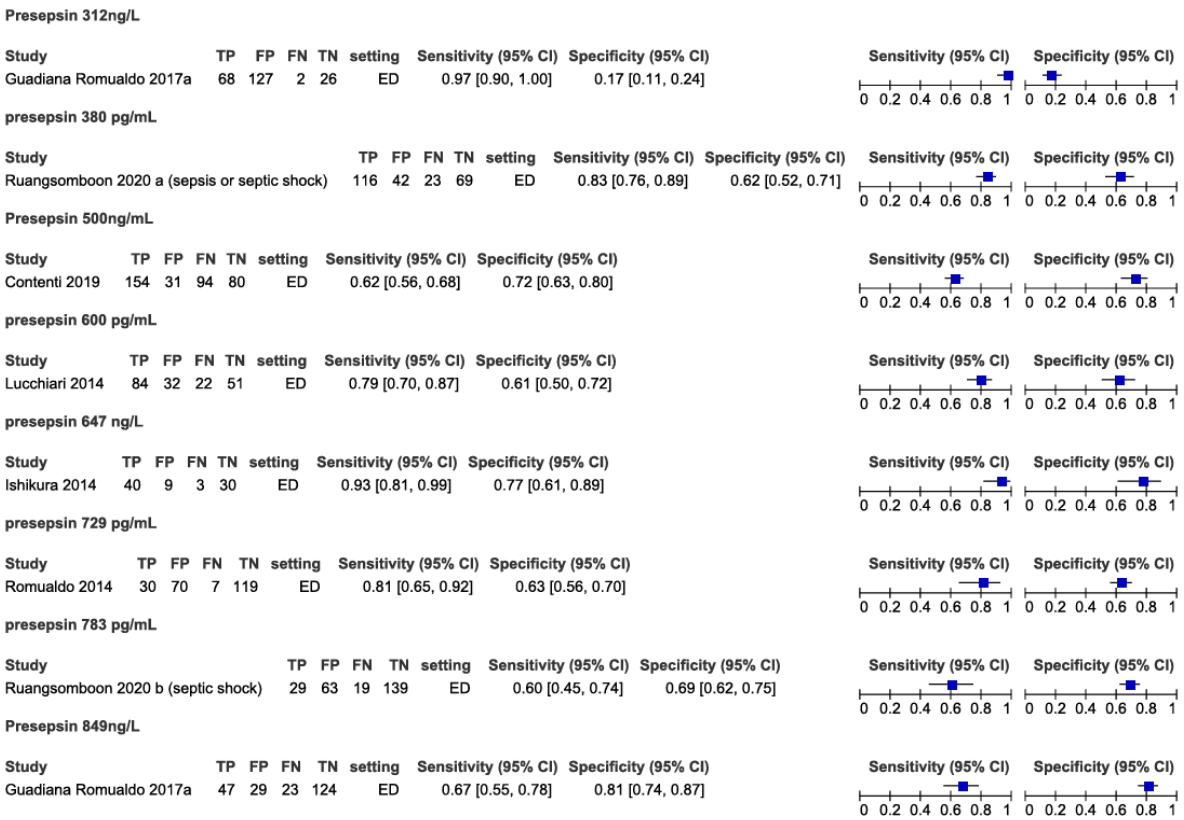
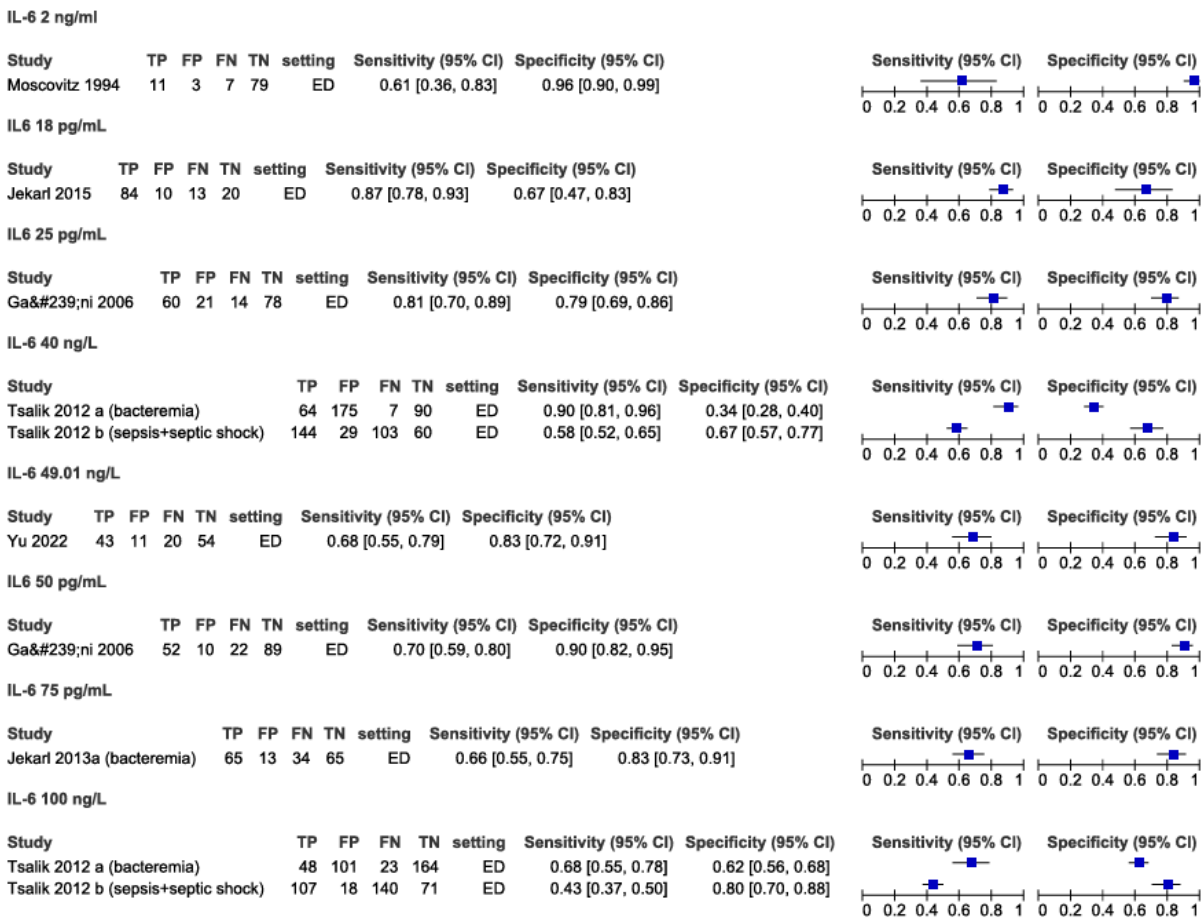
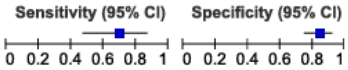


Figure 22: Sepsis: Forest plot for IL-6



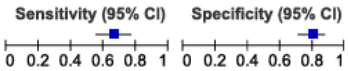
IL6 120ng/L

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Lin 2000	16	12	7	65	ED	0.70 [0.47, 0.87]	0.84 [0.74, 0.92]



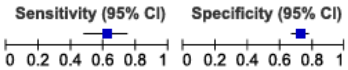
IL-6 145 pg/mL

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Jekarl 2013b (severe sepsis/septic shock)	52	20	26	79	ED	0.67 [0.55, 0.77]	0.80 [0.71, 0.87]



IL-6 209 ng/L

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Tromp 2012	34	80	21	207	ED	0.62 [0.48, 0.75]	0.72 [0.67, 0.77]



IL-6 500 ng/L

Study	TP	FP	FN	TN	setting	Sensitivity (95% CI)	Specificity (95% CI)
Tsalik 2012 a (bacteremia)	19	28	52	237	ED	0.27 [0.17, 0.39]	0.89 [0.85, 0.93]
Tsalik 2012 b (sepsis+septic shock)	35	3	212	86	ED	0.14 [0.10, 0.19]	0.97 [0.90, 0.99]

