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Review article

Biomarkers of inflammation in respiratory tract infections: a narrative review

ANDREA SARAČEVIĆ[1]*
HELENA ČIČAK[1]
LUCIJA DRINOVAC[2]

[1]Department of Medical Laboratory Diagnostics, Sveti Duh University Hospital, Zagreb, Croatia

[2]Department of Medical Biochemistry in Oncology, University Hospital for Tumors, Sestre milosrdnice University Hospital Center, Zagreb, Croatia

***Correspondence:**
Andrea Saračević
E-mail address: asaracevic@kbsd.hr

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Abbreviations

ARI	– acute respiratory infection
CFU	– colony forming units
COPD	– chronic obstructive pulmonary disease
COVID-19	– coronavirus disease 2019
CRP	– C-reactive protein
ESR	– erythrocyte sedimentation rate
ICU	– intensive care unit
LPS	– lipopolysaccharide
LRTIs	– lower respiratory tract infections
PCT	– procalcitonin
POCT	– point-of-care testing
RTIs	– respiratory tract infections
URTIs	– upper respiratory tract infections
WBC	– white blood cells

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Abstract

Background and purpose: *Respiratory tract infections (RTIs) are a global public health issue and one of the major causes of morbidity and mortality worldwide, especially in immune sensitive or compromised population. It is particularly challenging to distinguish viral from bacterial RTI based only on the symptoms presentations. Bacterial cultures are the gold standard in detecting the causative pathogens. However, they have several shortcomings such as variable diagnostic sensitivity, a relatively long turnaround time and the fact that not all possible pathogens can be detected using one culture. In such case, tests detecting host-response blood-based biomarkers are a valuable contribution in diagnosis making and patient management.*

Materials and methods: *A literature search was conducted in the PubMed electronic database from January 1st 2005 to March 31st 2025 using the following search terms "Clinical Laboratory Techniques" AND "Serum" AND "Infections" AND "Respiratory tract diseases" AND "Diagnosis" AND "Prognosis". Randomized,non-randomized studies as well as reviews were taken into consideration.*

Results: *C-reactive protein and procalcitonin are at the present the most robust and widely used biomarkers; however newer biomarkers such as serum calprotectin, pentraxin 3 and presepsin, as well as combinations of different biomarkers with high potential for clinical utility are emerging.*

Conclusions: *Host-response biomarkers of inflammation are useful tools in RTIs management when used together in conjunction with clinical symptoms. Depending on the kinetics of their release into the circulation and their elimination, they can be used as either early markers of inflammation or as a prognostic marker for disease severity and mortality.*

INTRODUCTION

Respiratory tract infections (RTIs) are defined as any infectious disease of the respiratory system *(1).* They include a wide range of diseases that affect the upper and lower respiratory tract, starting from a common cold, laryngitis, pharyngitis/tonsillitis, acute rhinitis/rhinosinusitis up to more complex and severe diseases such as bronchitis and pneumonia. Overall, RTIs are a global public health issue and are a cause of significant burden on healthcare system. They are one of the major causes of morbidity and mortality worldwide, especially in children younger than 5 years, elderly population over 70 years of age, immunocompromised individuals and those with multiple comorbidities *(2).* Therefore, it is of great importance to identify the causative

agent(s) on time, not only to prescribe adequate therapy to the patients, but also to determine disease severity, prognosis and if possible to eliminate or to predict undesirable adverse patient outcomes. It is particularly challenging to distinguish viral from bacterial RTIs based only on the clinical symptoms. Unnecessary antibiotics prescriptions, not only burden national health care systems for millions of pounds on a yearly basis *(3),* but can additionally cause drug-related adverse events and lead to increased prevalence of antibiotic-resistant organisms in the local/global community *(2).* The current gold standard for detecting most typical bacterial pathogens is the body fluid/tissue microbiology culture. Unfortunately, microbiology cultures have several limitations - all possible causative pathogens cannot be detected using one single culture, they are slow and time consuming (turnaround time at least 2-3 days) and their sensitivity varies depending on the applied thresholds of colony forming units per milliliter (CFU/mL) *(4,5).* For example, in a clinically diagnosed pneumonia, when utilizing a low threshold of 1,000 CFU/mL, broncoalveolar lavage fluid culture sensitivity varies between 80% and 90% *(6,7,8*), whereas it reduces to as low as 16% *(9)* or 55 *(8)* when utilizing the threshold of 100,000 CFU/mL. In such cases, blood based biomarkers, in conjunction with clinical presentation, can provide significant help to the clinicians as a useful contribution in diagnosing and patient management. In an ideal scenario, a valuable biomarker

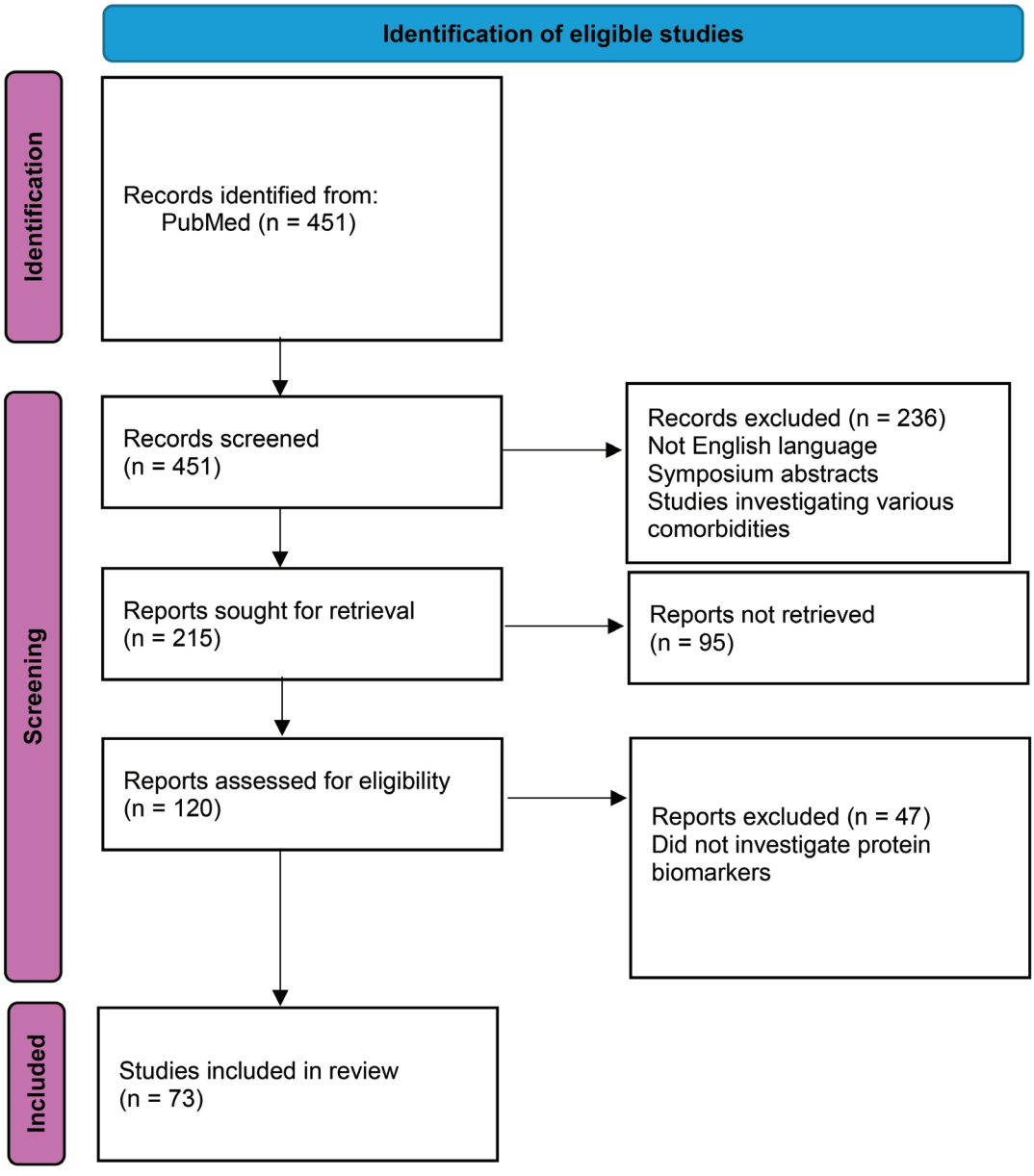

Figure 1. *PRISMA flow diagram for selecting eligible studies*

would have several important characteristics such as high sensitivity and specificity, ability to be collected non-invasively, easily-measured, consistent, quantitative and reliable measuring analytical methodology and affordable price *(10)*. Unfortunately, at the present there is no ideal biomarker; however there are several biomarkers that, despite their shortcomings, have significant advantages that make tham clinically very important and useful.

The aim of the present narrative review is to summarize the characteristics of the most useful and promising protein-based inflammation biomarkers, as well as their combinations in RTIs.

MATERIALS AND METHODS

A search was conducted in the PubMed electronic databasesfrom January 1st 2005 to March 31st 2025 using the following search terms "Clinical Laboratory Techniques" AND "Serum" AND "Infections" AND "Respiratory tract diseases" AND "Diagnosis" AND "Prognosis". We considered randomized,non-randomized studies as well as reviews published in peer-reviewed journals with a Journal Citation Reports Index; studies published in English. The search revealed a total of 451 results in PubMed. The flow diagram of selecting eligible studies is presented in Figure 1. First, two authors identified potentially relevant studies by reviewing titles and abstracts. After retrieving full articles, the third author reviewed all of them (N = 120) to determine their suitability for further analysis. Finally, 73 full articles were included in this narrative review.

RESULTS

Based on the literature search, we identified C-reactive protein (CRP), procalcitonin (PCT), calprotectin, pentraxin 3 (PTX3) and presepsin as useful and promising biomarkers whose characteristics are presented in this narrative review. The basic characteristics of the biomarkers are presented in table 1. We also describe different combinations of biomarkers whose role in RTIs was recently intensively investigated in different clinical settings.

C-reactive protein and procalcitonin

C-reactive protein is a member of the pentraxin family, a highly conserved class of pattern recognition molecules. CRP is composed of five identical non-covalently bound subunits forming a pentamer that has two different binding sites: A-face that binds and activates complement C1q; and B-face contains the Ca^{2+}-dependent binding pocket for phosphocholine, expressed by bacterial, fungal and eukaryotic cells *(11,12,13)*. CRP also binds many other ligands including nuclear antigens, oxidized LDL receptor, apoptotic cell membrane etc. *(11,12,13)*. Induction of the CRP gene transcription occurs in the liver in response to increased levels of inflammatory cytokines, especially interleukin 6 (IL6), interleukin 1β (IL1β) and tumor necrosis factor α (TNFα) *(11)*. Since CRP is an acute-phase protein, its plasma concentration deviates by at least 25% during inflammatory processes *(14)* and increases up to 1,000-fold with some bacterial infections *(15)*. However, when the stimuli end, CRP values decrease exponentially over 18–20 h, close to the half-life of CRP *(16)*. Increased CRP concentrations are typically associated with disease, but liver failure is one condition observed to impair CRP production *(16)*. Very few drugs reduce elevated CRP levels unless they treat the underlying pathology that is causing the acute-phase stimulus. There is emerging research that oral hormone replacement therapy causes background levels of circulating CRP to increase in postmenopausal women, increasing the risk of thrombotic events such as clots *(16)*.

Procalcitonin is a protein that consists of 116 amino acids and is the peptide precursor of calcitonin. PCT concentrations rise in response to bacterial infections. Levels are detectable at 4 hours, peak at 6 hours and maintain a plateau through 8 and 24 hours before they decrease rapidly when the infection is under control, but they are not affected by the use of anti-inflammatory drugs, including corticosteroids (17). In healthy individuals, PCT is produced in the thyroid C-cells, cleaved from pre-procalcitonin by an endopeptidase in the endoplasmic reticulum. PCT is then further broken down to form N-terminal PCT, C-terminal katacalcin and active calcitonin. As all the PCT formed in the C-cells is broken down into the above-mentioned products and no PCT enters the circulation, the serum PCT concentration in healthy subjects under physiological conditions is very low (<0.1 μg/L) (18). Moreover, with a half life of 25-30 hours, it remains unchanged within the circulation since it is resistant to plasma enzyme changes/degradation (19). Several studies have shown the production of PCT in response to bacterial lipopolysaccharide (LPS) or other endotoxins and to inflammatory markers like IL-β, IL-6, TNF-α, IL-2, etc. The presence of PCT in the serum of thyroidectomized patients during bacterial infection supports the notion that an organ other than the thyroid is the source of PCT. Serum levels of PCT increase in patients with impaired renal function (19). Considering the high incidence of renal failure in patients admitted to hospital and critical care units, the utility of PCT might be limited (19), although one large individual patient meta-analysis suggested that use of PCT in patients with impaired kidney function works well and is associated with shorter antibiotic courses and lower mortality rates (20). Diagnosis of the type of bacterial or a viral infection mainly need the support of bacterial culture, nucleic acid test or antibody detection. The culture process is time-consuming, nucleic acid test may cause missed detection due to sample collection problems, while antibody detection is affected by factors such as infection time, antibody concentration

and insufficient sensitivity of the detection method. For different types of infections, clinical medications are also different. Experiential medication is a common clinical treatment, and it is also one of the causes of antimicrobial drug abuse and bacterial resistance. It is an urgent problem to quickly distinguish the types of infection and guide clinical accurate drug use (21). CRP and PCT remain the most robust and widely used biomarkers for respiratory tract infections. However, PCT has a number of limitations. It is elevated in a variety of noninfectious conditions, such as cirrhosis, pancreatitis, mesenteric infraction, burns, and aspiration pneumonitis (22). Additionally, its diagnostic and predictive value declines in patients with severe sepsis and in localized infections (e.g. endocarditis, empyema) (22). PCT has a high negative predictive value for exluding bacterial infections (23). If PCT is negative, it is highly unlikely there is a systemic inflammatory reaction due to bacteria. The PCT trend over time can be monitored to gauge clinical improvement of a bacterial infection. As the concentration decreases, the prognosis improves. Data shows that PCT is not elevated during common community-acquired acute respiratory infection (ARI), yet CRP concentrations show a higher variability (24). This is also consistent with findings from other primary care studies, suggesting that PCT is more specific to bacterial infections and its concentrations are low in patients with mainly viral infections, while CRP increases independently of infection type as a "systemic inflammatory marker". Generally, ARIs are mild to moderate in severity, requiring neither healthcare services nor prescription of medications, and are often viral in etiology (24, 25). Most of the relevant studies have concluded that serum PCT levels may be useful for predicting the prognosis of patients with lower respiratory tract infections (LRTI) but do not perform better than classical laboratory methods and clinical scores. The combined detection of leucocytes (i.e. white blood cells, WBC), PCT, CRP and erythrocyte sedimentation rate (ESR) has a predictive value in detecting the occurrence of complications in patients with community-acquired LRTIs (26). Therefore, in this scenario, PCT should be regarded as an additional parameter that increases the accuracy of classical methods but has limited value when used alone. The use of PCT seems most useful when low PCT levels are detected, enabling the identification of patients with a lower risk of adverse outcomes. In terms of practical applicability, low levels of PCT in patients without an obvious indication for intensive care would increase confidence in the decision to maintain them outside of the intensive care unit (ICU) (27). A large prospective cohort study of 1770 adults revealed that PCT is strongly associated with the risk of requiring invasive respiratory or vasopressor support (28). In patients with chronic obstructive pulmonary disease (COPD), elevated PCT levels can help distinguish between acute onset and stable COPD (29). However, a literature review suggested that the current available evidence is still relatively weak, and further research is needed. The cut-off value of PCT is yet to be determined to assist in the clinical determination of acute COPD (30). Radiologically confirmed pneumonia is not associated with respiratory virus detection. Moreover, in the studied episodes of hospital care diagnosed with pneumonia, the presence of a respiratory virus is associated neither with clinical outcomes, nor with WBC or CRP values. Radiologically confirmed pneumonia is in fact associated with the indicators of a severe bacterial infection, WBC over 15×10^9/L and CRP over 100 mg/L (31). CRP value over 100 mg/L is associated with death at ward (31). In the light of the recent pandemic, inflammatory biomarkers are strongly associated with the severity of the disease for Coronavirus disease 19 (COVID-19). For example, Liu and colleagues found IL-6 and CRP to be independent predictors of disease severity in COVID-19 patients (32). They show high discriminative accuracy to predict the need for hospitalization in patients with COVID-19 (32). At present, CRP is the only biomarker available for point-of-care (POCT) test in primary care settings, where evidence supports that it can guide antibiotic prescriptions for ARIs. POCT devises for CRP are applicable in primary care, as test results are provided within 2 to 3 minutes (33). While the use of CRP measurements with POCT devices reduces antibiotic prescribing by up to 42%, additional studies in primary care have demonstrated that combining CRP POCT with communication skills training can significantly increase this impact (34). The main challenge to be addressed for biomarkers is consensus on a diagnostic threshold. With regards to CRP, one of the largest diagnostic European studies conducted in adults, identified a threshold of 30 mg/L as the best cut-off to be combined with signs and symptoms for ruling out severe bacterial infection and to avoid the misuse of antibiotics (35). Previous systematic reviews found that CRP >20 mg/L is of value in diagnosing bacterial pneumonia. In one meta-analysis CRP >10 mg/L described the best performance in terms of sensitivity (90%) in contrast with specificity (42%) (36). The Danish College of General Practitioners' guideline for managing patients with acute RTIs states that if the CRP value is >50 mg/L, antibiotics should be considered (37). The use of PCT embedded in clinical algorithms has the potential to improve the antibiotic management of ARI patients and has substantial clinical and public health implications to reduce antibiotic exposure and the associated risk of antibiotic resistance. The diagnostic performance of PCT>0.1 μg/L is overall acceptable (with sensitivity and specificity of 74%) (36, 38).

Calprotectin

Calprotectin is a heterodimer that belongs to the S-100 protein family. Most of the soluble cytosolic protein in neutrophils represents calprotectin and can be considered as an early marker for neutrophil activation and mediated inflammation due to its release from the neutrophils.

Moreover, the calprotectin was also detected in different concentrations in various cells such as monocytes, macrophages, epithelial cells etc. *(39).* Also, calprotectin has a role in various processes in lung health and diseases including anti-microbial, pro- and anti-tumor functions, angiogenesis and extracellular matrix remodeling. Because calprotectin is not synthesized *de novo* as some acute-phase proteins it can potentially meet some criteria for a great local marker of inflammation *(40).* Havelka and colleagues have found increased calprotectin concentrations in patients with bacterial infections and the authors implicate that calprotectin could be a better marker over procalcitonin for diagnosis of bacterial respiratory infections *(41).* According to the literature, calprotectin may have further clinical use as a marker for distinguishing bacterial respiratory tract infections from viral infections *(42).* Moreover, the role of calprotectin has also been investigated in recent COVID-19. De Guadiana-Romualdo and co-workers have reported that calprotectin has high diagnostic accuracy as a marker that can help determine which patients admitted to the emergency department will require invasive mechanical ventilation and/or admission to the intensive care unit *(43).* Also, several literature data show that calprotectin could be used as a predictable marker for COVID-19 severity and the ability to discern the need for invasive respiratory support in COVID-19 patients *(44,45,46,47).* Due to the strong link between inflammation and malignant disease, calprotectin could have a great diagnostic value in the early diagnosis of lung cancer *(48).* Additionally, calprotectin concentration may be used as an indicator of endothelial injury and determination of the severity of obstructive sleep apnea (OSA) in both adults and children *(49,50).* Interestingly, calprotectin has shown a positive association with the severity of community-acquired pneumonia (CAP) not only in adults but in children as well *(51).*

Calprotectin concentration can be measured in both serum and plasma, but it can also be found in measurable concentrations in various body fluids such as sputum and pleural fluid. Some studies indicate that calprotectin measured in sputum samples can be used to monitor antibiotic therapy in patients with cystic fibrosis or distinguish malignancy in pleural fluid *(52,53).* Calprotectin could also be measured in bronchoalveolar lavage fluid in patients with CAP *(54).*

Pentraxin 3

Pentraxin 3 belongs to the family of pentraxins which are divided into two groups, long and short pentraxins. C-reactive protein belongs to the short pentraxins, and pentraxin 3 belongs to the long pentraxins *(55).* Pentraxin 3 is a mediator of innate immunity and is rapidly produced by various cells e.g. macrophages, endothelial, dendritic cells etc. as a response to inflammation *(56).* As well as calprotectin, pentraxin 3 is locally produced at the site of inflammation and may be considered a specifically good marker for various diseases with inflammatory pathophysiology. Moreover, concentrations of pentraxin 3 peak much earlier (6-8 hours) than the CRP whose peak concentration is at 24 to 48 hours, which is one of the desirable characteristics for a great biomarker *(57).* According to He and colleagues, pentraxin 3 has the potential to be a marker of acute lung injury *(58).* Literature data showed that plasma concentration of pentraxin 3 is increased in patients with CAP and the concentration decreased in patients who received antibiotic therapy. Also, pentraxin 3 may be a prognostic marker due to shown significant correlation with the hospitalization time *(27, 59).* Moreover, pentraxin 3 could be used for prognosis and monitoring lung cancer, tuberculosis as well as in diagnosing aspergillosis *(60,61,62).* Pentraxin 3 can be used for distinguishing parapneumonic effusion from other exudative effusions *(63).* Increased levels of pentraxin 3 were found in patients with acute respiratory distress syndrome and can be used as a prognostic marker for disease severity and mortality *(64).* Pentraxin 3 could also be used as a marker of endothelial injury and a predictor of mortality in COVID-19 patients *(65,66).* On the other hand, pentraxin 3 can be measured in body fluids such as bronchoalveolar fluid where pentraxin 3 is shown as a reliable biomarker of ventilator-associated pneumonia or can be measured in sputum in asthmatic pediatric patients and used as a marker for disease severity *(67,68).* Additionally, pentraxin 3 can be a promising marker for diagnosis, prediction of severity, and prognosis of lower respiratory tract infections in children *(69).* Literature showed a correlation between increased concentrations of pentraxin 3 with fever duration in children with lower respiratory tract infections and that pentraxin 3 is a more sensitive marker than the most commonly used CRP *(70).* In children with asthma, increased concentrations of pentraxin 3 in sputum are found and it could be used as a biomarker for disease evaluation *(53).*

Presepsin

Presepsin or soluble CD14 subtype (sCD14-ST) is a promising biomarker that can be used for the diagnosis of infections at an early stage. As respiratory diseases are one of the causes of mortality, presepsin could be a promising biomarker to differentiate the etiology of pneumonia (e.g. bacterial pneumonia) or can be used for the determination of disease severity *(71,72).* Also, presepsin is considered as a promising early marker of inflammation compared to CRP and PCT due to the concentration increase in the first two hours after the beginning of inflammation (73). Some literature data has shown that the presepsin could be used as a predictive marker for CAP and mortality of the disease *(74,75).* Increased presepsin concentrations could also be used for diagnostic purposes for pulmonary tuberculosis and CAP *(76).* Additionally, presepsin may predict the mortality risk in severe COVID-19 patients due to elevated cytokines (e.g. mac-

rophage inflammatory protein 1a) that stimulate further production of presepsin *(77, 78)*. Halici and co-workers also showed that the presepsin may be used as a diagnostic biomarker of pneumonia in patients with chronic obstructive pulmonary disease *(79)*. In pediatric population, presepsin has been shown as a useful marker for determining the severity of CAP and the diagnosis and prognosis of pneumonia *(80)*. Interestingly, measurable concentrations of presepsin could be found in tracheal aspirate and may be also used as an early marker of pneumonia in the neonatal population *(81,82)*.

Combinations of biomarkers

Even though protein biomarkers can give certain aid in RTIs management, measuring only one at a time has its limitations due to variable sensitivity in different diseases as well as different kinetics in certain viral and bacterial infections. Therefore, several studies have investigated the combinations of differet combinations of biomarkers (both laboratory and POCT methodology) in managing RTIs in various clinical settings.

For instance, Ingram and his co-workers investigated the combined diagnostic accuracy of CRP and PCT in 25 patients admitted to the ICU with community-acquired pneumonia. They found that a PCT cutoff of >0.8 µg/l and CRP >200 mg/l had sensitivity 100%, specificity 94%, negative predictive value 100% and positive predictive value 90% for detection of patients with bacterial/mixed infection *(83)*. Their conclusion suggested that low concentrations of both markers, identifies patients with no need for antibiotics prescription when considered with clinical symptoms. Additionally, another study investigated of both CRP and PCT, as well as their combination in distinguishing between viral and bacterial LRTIs in 209 patients *(84)*. Their cut off values were 22 mg/L for CRP or 0.18 µg/l for PCT with respective AUC 0.77 (95% CI: 0.70–0.84) and 0.74 (95% CI: 0.66–0.82). The AUC for their combination was 0.77 (95% CI: 0.70–0.84), showing that the combination of CRP and PCT did not provide added value when compared to a single biomarker measurement.

In addition, POCT methodology incorporating the combination of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), interferon-γ-induced protein 10 (IP-10) and CRP or the combination of CRP and myxovirus resistance protein-1 (MxA) in different types of RTIs was also investigated. These POCT devices are easy-to-use with relatively fast turnaround times, and they provide prompt results that could have potential clinical utility in discriminating the viral vs. bacterial etiology of RTIs. The studies were designed either as cohort studies, or nested case-control studies. Depending on the patient population included into the studies as well as on the studied RTIs, the diagnostic specificity and sensitivity for TRAIL, IP-10 and CRP varied between 60% - 100% and 70 - 100%, respectively *(85)*. For the combina-

Table 1. *Basic characteristics of blood based biomarkers of inflammation in respiratory tract infection*

Biomarker	C-reactive protein	Procalcitonin	Calprotectin	Pentraxin 3	Presepsin
Basic characteristics	acute-phase protein synthesized by the liver in response to interleukin 6	prohormone, synthetized in virtually all organs in response to inflammatory stimuly	a calcium- and zinc-binding protein of the S-100 protein family which is mainly found within the cytoplasm of neutrophils	acute phase protein, produced by multiple cells type in response to inflammatory mediators	a 13 kDa fragment of CD14 molecule involved in the innate immune response
Time for concentration elevation(hours)	4-6	3-4	2*	rapidly	1-2
Time of concentration peak (hours)	36 – 50	24	24-36*	6-8	2-4
$T_{1/2}$ (hours)	19	22-35	5	1-4	4-5
Advantages	not affected by immunosupression (steroids/ neutropenia)	not affected by immunosupression (steroids)	NA	prognostic value in critically ill patients with SIRS, sepsis, or bacteremia	Promising biomarker for bacterial infections and sepsis diagnosis
Shortcomings	low synthesis in patients with fulminant hepatic failure	caution with results interpretation in patients with neutropenia, acute kidney injury associated and renal replacement therapy	currently clinically validated for rheumatoid arthritis	NA	NA

*Kinetics after inguinal hernia surgery
NA – not applicable (still in the phase of active research)

tion of MxA and CRP the specificity and sensitivity ranged 73-98% 61–100%, respectively *(72).* Taken altogether, the study designs, the eligibility criteria, methodology and statistical analysis applied, due to significant proportion of studies with high risk of bias, it is not possible to draw valid and strong conclusions. Nevertheless, this only highlights the need for future high-quality, well-designed research that will examine not only the clinical utility of individual biomarkers or their combinations, but also their effectiveness and overall cost-effectiveness in both in and out-patient settings.

CONCLUSION

Protein based biomarkers of inflammation are useful tools in RTIs diagnosis and management when used in conjunction with clinical disease presentation. CRP and PCT are the most widely used biomarkers of inflammation in everyday clinical practice.

According to the available literature, there are numerous studies of new biomarkers for determining inflammation in certain conditions to establish the presence of inflammation as early as possible and better understand the impact and the degree of inflammation in certain diseases. Calprotectin and pentraxin 3 have shown excellent potential as local biomarkers in inflammatory conditions, while presepsin can be used for prompt detection the inflammation compared to CRP and PCT.

Using solely biomarkers concentration for distinguishing between viral and bacterial diseases is not recommended since there can be overlapping in their concentrations depending on disease stage, presentation, severity and the presence of one/more comorbidities. Depending on the kinetics of their release into the blood stream and their elimination, they can be used as either early markers of inflammation or as a prognostic marker for disease severity and mortality. Also, there is a need for further research to determine whether any of the new biomarkers can reliably distinguish the etiology of inflammation and detect it as early as possible in order to rationalize the use of antibiotics and rapidly introduce the necessary therapy to improve the patient's outcome. Further research could show whether there is a combination of new and/or routine markers of inflammation that would have the highest diagnostic accuracy and could even be integrated into point-of-care tests.

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