

Manuskrip CRP dan Procalcitonin.

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Submission date: 05-Nov-2023 04:55AM (UTC+0000)

Submission ID: 214788509

File name: Manuskrip_CRP_dan_Procalcitonin.docx (2.1M)

Word count: 3767

Character count: 22672



The Role of C-Reactive Protein and Procalcitonin as Biological Markers of Inflammation for Bronchoscopic Procedures

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Abstract

Background:

In the respiratory system, bronchoscopy is a basic procedure utilized for both diagnostic and therapeutic purposes. In spite being a generally safe procedure, bronchoscopy can result in complications that range in severity from moderate to severe. Pulmonary infection is among the potential complications that can happen after to a bronchoscopy procedure. An incidence of 0.2% to 5.2% has been described typically for complications such as empyema, lung abscess, and pneumonia that may develop after bronchoscopic procedures. Although these complications are uncommon, their prognosis can be quite bad. The risk of pulmonary infection, specifically pneumonia, has been related in several studies to sepsis and mortality in patients enduring bronchoscopic procedures.

The initiation of the infection exposure process into the lung can be assisted through a variety of factors, including the underlying diagnosis and the type of intervention performed during the bronchoscopy procedure. A critical complication that needs additional consideration is the potential transmission of infection through bronchoscopy procedures. It is beneficial to consider prophylactic antibiotics prior to a procedure due to the possibility that infectious agents will be transferred from one patient to another. Antibiotic prophylaxis may involve the utilization of C-Reactive Protein (CRP) and Procalcitonin (PCT) testing as determining parameters. Since an effective and alternative predictive parameter prior to bronchoscopy procedures, the proinflammatory mediators CRP and PCT are now utilized in tandem with developments in science in recent years.

Keywords: CRP, PCT, Bronchoscopy, Biological, Markers

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INTRODUCTION

Bronchoscopy is an intervention in medicine that provides tracheobronchial visualization by placing optical instruments into the airway. Bronchoscopy is a relatively safe procedure with a morbidity rate of 2.5% and a mortality rate smaller than 0.05%. Bronchoscopy is a significant interventional procedure used in the diagnosis and staging of cancer patients and plays a role in interstitial and infectious diseases. Based on the shape

and nature of the instrument, there are two types of bronchoscopy: rigid bronchoscopy and flexible fiberoptic bronchoscopy (FOB)/ flexible bronchoscopy.¹

Generally, an experienced bronchoscopy operative conducts rigid bronchoscopy under general anesthesia in the operating room. If rigid bronchoscopy is considered beneficial or when all other alternatives are exhausted, it ought to be executed. In the emergency room, endoscopy suite, operating theater, or intensive

care unit, flexible bronchoscopy may be performed. The auxiliary equipment on the flexible bronchoscope is superior and its working channel is more expansive. The method of identifying FOB is dependent upon the patient's clinical condition, the size and location of the lesion, and the presence of metastases.²

The impact of various bronchoscopic procedures, including but not limited to forceps biopsy, endobronchial needle aspiration, bronchial brushing, and bronchial washing, and the combination of these procedures, on the secretion of inflammatory mediators remains inadequately investigated. Bronchoscopic examination may also serve as an entry point for an infection to reach the body.³ Identifying between infections rapidly and accurately requires the utilization of suspected clinical observations and analysis of inflammatory biomarkers. Antibiotics administered early in the progression of infectious diseases can decrease both mortality and morbidity. By conducting a thorough analysis of inflammatory biomarkers, the incidence of antibiotic resistance can be reduced due to the decreased inappropriate use of antibiotics.⁴

The acute phase response induced by bronchoscopy becomes measurable for 24 hours following the procedure. Acute phase response can be identified by an increase in fibrinogen in 25%, neutrophils in 50%, and C-reactive protein (CRP) by more than 7-fold. Furthermore, there will be a 25% increase in serum ferritin concentrations, accompanied by a decrease in total iron binding capacity, transferrin saturation, and serum iron levels. It indicates that the homeostatic dysregulation between iron and interleukin 8 (IL-8) remains

unchanged. Acute phase response is a syndrome characterized by systemic metabolic and neuroendocrine alterations in addition to an acute inflammatory response. Alterations in hepatic synthesis of several plasma acute phase proteins, fever, sleep, the release of adrenocorticotropin and cortisol, and the activation of B-cells and T-cells are all potential modifications.⁵

It is thought that the acute phase response is an adaptive mechanism that enables an increase of inflammation, eventually leading to optimal healing. Several studies show that febrile events transpire in approximately 48% of cases following to bronchoscopy. Fever is characterized by increased levels of CRP, procalcitonin (PCT), and neutrophils in the patient. Fever attributed to an infection contributed to 2.56% of cases reported after bronchoscopy with bronchoalveolar lavage (BAL), while the prevalence of fever following bronchoscopy with BAL was 5.12%. PCT shows a sensitivity of 81% and a specificity of 84% when measured at a 0.5 ng/ml level. PCT and IL-8 levels can be used as biomarkers to determine antibiotic therapy prior to the availability of culture results, according to the study's findings. PCT and proinflammatory cytokines should be measured 24 hours after a bronchoscopy with BAL.³⁻⁵

Wang et al. (2019) recommended that in order to predict endobronchial biopsy (EBB)-induced hemorrhage in patients with lung cancer, a CRP test be performed prior to BSOL. This study found that the CRP levels of the bleeding group were substantially higher than those of the non-bleeding group. With a specificity of 31.2% and a sensitivity of 94.04%, the CRP threshold value is 1.15 mg/L. This

value determines whether a biopsy is undertaken and how bleeding is managed throughout EBB.⁶

There is a correlation between an excessive systemic inflammatory response following FOB and increased morbidity and mortality. These figures typically apply to bronchoscopies conducted on adults without sedation; thus, moderate sedation is needed. Sedation that is deep can accelerate the onset of fever following a bronchoscopy.⁷ The routine evaluation of CRP and PCT by a clinician is especially beneficial during the 24–96 hours period following the procedure. Complications post FOB require further treatment.⁵ Bronchoscopy-related complications include hypoxemia (0.7–76.3%), hemoptysis (2.5–9%), and fever (2.3–33%). Pneumonia incidence following bronchoscopy varies among 0.02–6.3%.^{8,9} Shimizu et al. (2020) found which 3.0% of bronchoscopies were associated without death or non-disabling infectious complications.¹⁰

CRP and PCT measurements are used as screening instruments during bronchoscopy procedures with the aim to anticipate the development of infectious complications following the procedure, given the prior situation. As the potential for an increase in inflammatory biomarkers is important, it is anticipated that this review article will serve as a resource for preventing severe complications following bronchoscopy.

STRUCTURE AND MECHANISM OF C-REACTIVE PROTEIN

In 1930, Tillet and Francis first identified the CRP test. The term CRP was derived from the finding that it initially reacted with the

carbohydrate "C" antigen of the pneumococcal capsule in the serum of patients exhibiting acute inflammation. CRP is a tissue damage-sensitive, nonspecific inflammatory mediator that is susceptible to bacterial infection. Minimal quantities of CRP (1 mg/L) are detected in normal serum as an acute phase protein. Increases 100-fold in CRP levels may result from inflammatory responses or tissue injury induced by infectious or non-infectious diseases. Tumor necrotic factors – (TNF)- α , IL-6, and TNF- α are cytokines that stimulate CRP production.¹¹

3
CRP is rapidly synthesized in the liver in response to a mild trigger; the serum concentration approaches 5 mg/L within 6–8 hours, and peaks between 24–48 hours later. With a 19 hours half-life in plasma, the substance remains detectable in both healthy and diseased individuals. The measurement of CRP levels in the bloodstream via the calculation of IL-6 synthesis provides a direct indication of the pathological mechanism responsible for CRP production. After the inflammatory process or tissue injury has been resolved, CRP levels will decrease significantly and return to normal within 24–48 hours. Plasma levels of CRP will stabilize and remain unaffected by diurnal variations. Blood CRP concentrations can only be regulated through the synthesis process, as the clearance rate maintains constant.^{11–13}

Opsonin activity against microbes, parasites, and immune complexes is the function of CRP. CRP measurement in a serial pattern can be utilized to diagnose infection, measure response to therapy, and detect recurrent cases early. CRP is an indicator of the severity of systemic inflammation and is

mainly produced in the liver in response to inflammation. After a variety of conditions, including injuries, infections, neoplasms, arthritis, acute trauma, infarction, and surgery,

the acute phase response is observed. It has been shown that acute phase responses can be induced by normal physiological processes, including pregnancy and exercise.¹⁴

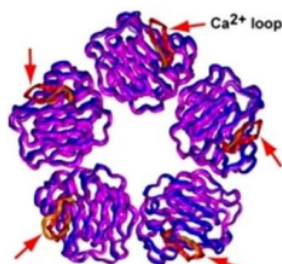


Figure 1. Structure of C-Reactive Protein

CRP elevations are classified as a marker of acute inflammation despite the fact that they are recognized as a nonspecific occurrence during acute inflammation and likely malignant processes. However, an increasing amount of studies are beginning to suggest that it may also have an important role in chronic inflammation.¹² The sensitivity and specificity of CRP levels are greater than those of the absolute total lymphocytes ratio and total neutrophil cell. As an inadequate protective mechanism against microbial invasion or trauma, inflammation damages tissues and destroys or restricts the presence of hazardous substances. Although inflammation is required to defend the body against numerous threats that upset equilibrium, it can also repair structural damage and impaired tissue function.^{13,14}

As shown in Figure 1, the homopentameric calcium-binding protein structure of CRP, also referred to as native CRP (nCRP) or pentamer CRP (pCRP), irreversibly dissociates at the site of inflammation into monomer CRP (mCRP).

nCRP and mCRP are two isoforms of CRP that differ in that nCRP generally exhibits greater anti-inflammatory activity than mCRP. As shown in Figure 2, the nCRP isoform stimulates phagocytosis, prompts apoptosis, and activates the classical complement pathway.^{11–14}

In addition to liver cells (hepatocytes), CRP is synthesized at various sites, including macrophages, smooth muscle cells, endothelial cells, lymphocytes, and adipose cells. Hepatocytes generate the nCRP isoform as an acute phase reaction in reaction to various stimuli, including infection, immunomodulators, and tissue injury. Monomeric form: derived from the dissociated CRP pentamer; extrahepatic cells, including adipose tissue, macrophages, and blood vessel smooth muscle, may also produce monomeric form. By enabling chemotaxis and directing leukocytes to the site of inflammation, the mCRP isoform prevents apoptosis. By inhibiting and inducing Nitric Oxide (NO) production, respectively, the nCRP and mCRP isoforms downregulate and upregulate Endothelial Nitric Oxide Synthase (eNOS).¹⁵

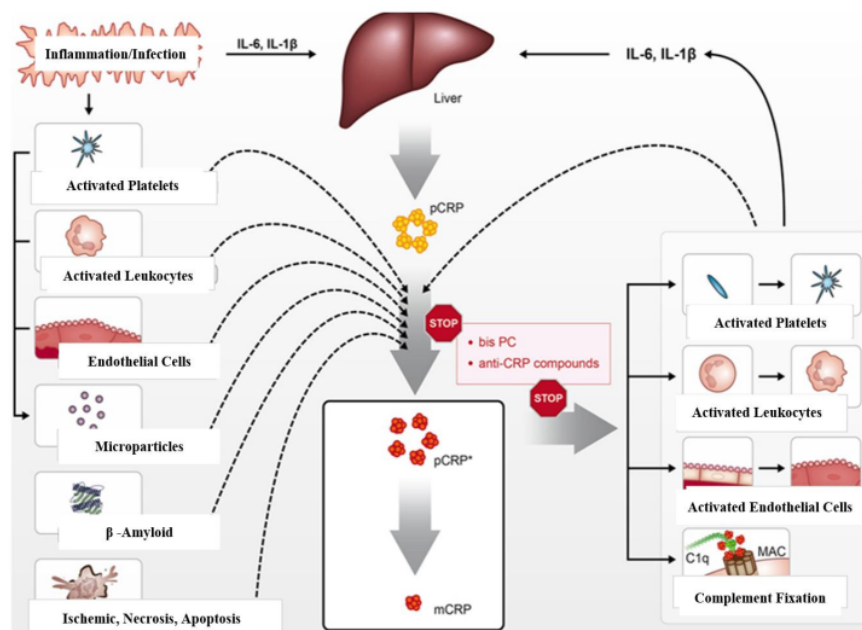


Figure 2: Role of CRP in the Inflammatory Process

STRUCTURE AND MECHANISM OF PROCALCITONIN

PCT prohormone levels were discovered to be significantly elevated in 1993 among sepsis patients and in numerous instances of severe Systemic Inflammatory Response Syndrome (SIRS), like burns, pancreatitis, pneumonia, extensive surgery, multitrauma, and conscious non-bacterial infections like malaria. From ten to hundreds and tens to thousands of times, these levels increase. As a prohormone, calcitonin PCT contains limited hormonal activity.¹⁶ In response to hypercalcemia or in patients with medullary thyroid cancer, the hormone calcitonin develops in the C cells of the thyroid gland, lung, and neuroendocrine cells. Calcitonin is a component of the prohormone PCT, which consists of 116 amino acids and contains 33 amino acids. The CALC-1 gene produces the

4 116-amino acid polypeptide procalcitonin.¹⁷
J Respir Indo Vol. xx No. x Januari 20xx

Samples of blood from healthy individuals contain intact PCT¹² calcitonin, NProCT (aminoprocaltitonin), CCP-1 (21-amino acid carboxyterminus peptide), katalcalcin, and CT C-terminal peptide (CCP)-1 attached to calcitonin. PCT consists of Calcitonin (CT), CCP-1, and an N-terminal peptide (N-ProCT) that is situated in its central region. The blood levels of intact circulating PCT in healthy individuals with N-PCT, CT, and CCP-1 components have low. The configuration of PCT is illustrated in Figure 3. Specific proteases convert PCT to CT, which is subsequently secreted in little amounts into the blood vessels. Normal individuals have plasma PCT concentrations below 0.05 ng/mL. In the presence of sepsis and severe bacterial infections, that number can multiply by a factor of 10,000.¹⁸⁻²⁰

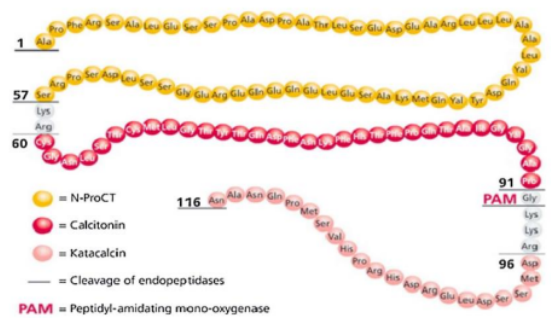


Figure 3. Structure of Procalcitonin

Sepsis and severe bacterial systemic infections are both critical diagnostic indicators that PCT can recognize. Proinflammatory cytokines produced by bacterial products, such as lipoteic acids emanating from gram-positive bacteria, endotoxins (LPS/Lipopolysaccharides) derived from the cell wall of gram-negative bacteria, and various components of necrotizing cells and microorganisms, stimulate PCT production.¹⁹ The sources of these substances could be endogenous migration of bacterial toxins or external infection. The stimulation of different toll-like receptor (TLR) pathways by Gram-positive and Gram-negative bacteria and fungi results in the generation of unique pro-inflammatory cytokines, that eventually stimulate the production of PCT. Consequently, it is foreseeable that distinct pathogens could cause various levels of PCT production.^{20,21}

The lack of a combination test for specific inflammatory biomarkers raises the likelihood of erroneous infection diagnosis, potentially leading to excessive antibiotic usage, delayed treatment, or unfavorable consequences.^{21,22} PCT has a significance level of 0.5 mcg/L for severe infection and 0.25 mcg/L for moderate mild infection. This may be taken into account as a result of the considerable Negative Predictive Value (NPV) of PCT and the high

sensitivity of CRP and PCT. PCT levels decline once bacterial infection is under control; it serve as an indicator of disease resolution. The addition of PCT to the comprehensive evaluation may serve as an addition to clinical and microbiological parameters.²³

MECHANISMS FOR INCREASED C-REACTIVE PROTEIN AND PROCALCITONIN

Fever indicates systemic inflammation caused by non-infectious etiologies or bacterial, viral, or parasitic infections.²⁴ Additionally, malignancy could contribute to fever. Based on their expertise, interviewing skills, and comprehensive physical examination, as well as the application of appropriate diagnostic tools such as microbiology and imaging tests, the clinician ought to possess the capacity to discern between febrile illnesses that are infectious and those that are not. In addition to the patient's initial symptoms and indications, biological markers can assist the clinician in determining the most suitable course of treatment. Additionally, targeted biomarkers enable the initiation of efficacious treatment.^{24,25}

After encountering the human body, bacteria secrete proinflammatory cytokines into the blood vessels, including IL-1 and IL-6, in reaction to the Pathogen Associated Molecular

Pattern (PAMP). Inflammation and damage to tissues Damage-Associated Molecular Pattern (DAMP) secreted by damaged tissue cells stimulate the production and release of IL-1 and IL-6 by immune cells through Toll-Like Receptor (TLR) signaling. It has been shown that these two cytokines trigger fever through connecting to IL-1 and IL-6 receptors, respectively, located on endothelial cells within the brain, with a particular emphasis on the hypothalamus. Interleukin-1 stimulates CRP production in the liver by inducing IL-6 synthesis, which includes hepatocytes and macrophages (Kupffer cells) in the liver. The following can be seen in Figure 4.²¹ Macrophages and dendritic cells are among the antigen presenting cells (APC) that are capable of identifying PAMP that are secreted into blood vessels following to bacterial infection.²⁶

Simultaneously, tissue injury or infection can induce inflammation via NETosis, which induces the discharge of DAMP. Several pattern recognition receptors (PRR) regulate the production of proinflammatory cytokines IL-1 and IL-6 through their recognition of DAMP and PAMP. Proliferating cytokines bind to specialized brain endothelium regions, which in turn produce prostaglandin E2 (PGE2), the principal mediator responsible for inducing fever. PCT production is stimulated by proinflammatory cytokines produced by bacterial products, such as endotoxins (LPS/lipopolysaccharides) produced by the cell wall of Gram-negative bacteria, lipotoxic acids from Gram-positive bacteria, and various microorganism components and necrotizing cells.^{25,26}

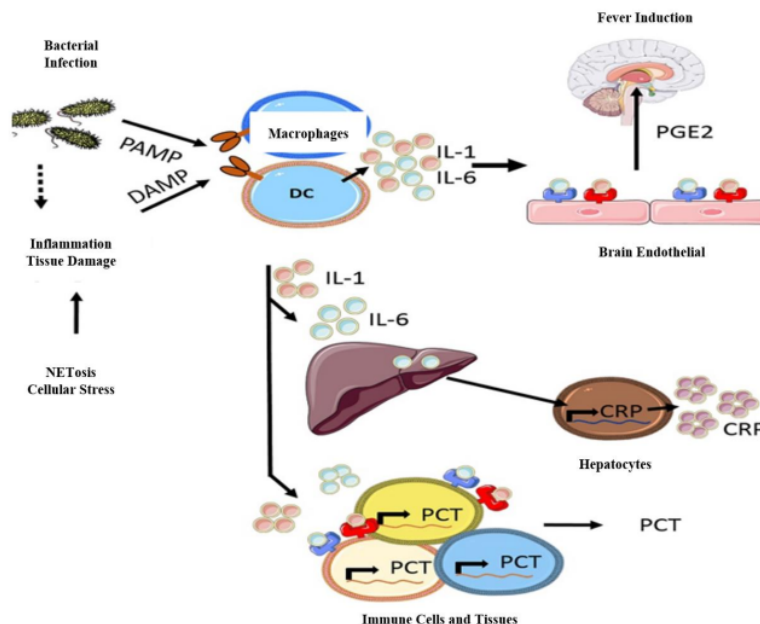


Figure 4. Description of Inflammation Induction and Release of Acute Phase Response Proteins

ROLE OF BIOLOGICAL MARKERS OF INFLAMMATION AFTER BRONCHOSCOPY

It has been reported that FOB with BAL can induce systemic inflammatory responses in

both healthy volunteers and patients.^{3,4} Fever is a common clinical manifestation observed in both pediatric and adult patients affected with diverse conditions. Patients that develop a fever following FOB need to have additional testing to determine the specific cause of the fever.²⁷ Although intensive, blood or sputum culture is the gold standard for identifying systemic bacterial infections. Alternative rapid predictive parameters that utilize inflammatory biomarkers such as CRP and PCT are widespread.³ Both CRP and PCT are accurate indicators for determining if antibiotic treatment is necessary.^{3,20} During bacterial illness and non-infectious inflammation, the levels of CRP and PCT increase.^{20,23}

Infections and inflammation can be detected early on in fever individuals using biomarkers such as CRP and PCT. These indicators are sensitive and specific, and therefore could be useful for disease monitoring.²⁰ Hackner et al. (2017) additionally suggested that damage to tissues triggers inflammatory reactions in the body as a whole and in particular regions. After this study was over, the different bronchoscopy methods that increase the risk of developing after bronchoscopy fever have been looked into. Pathogens could get in if the epithelium isn't strong enough. The treatments that were significantly related to fever (66.7%) were the process of the airways with forceps and argon plasma coagulation. Before and after the bronchoscopy, other procedures such as bronchial brushing and washing, hemoptysis management, balloon dilatation, airway inspection, lung volume reduction with valves, or various combinations of these procedures did not show any benefit.³

Early detection of individuals who need antibiotic treatment can be useful for their wellness. It's important to have biological markers and microbiological results in the lab for fever after a bronchoscopy. The fever people have higher levels of CRP, PCT, and neutrophils after the bronchoscopy operation. Finding out the PCT degree the day after a bronchoscopy can help with considering which antibiotics to apply. Fever after bronchoscopy occurred in 14% of the people that were studied, and in 25% of those cases, positive bacterial culture results in bronchial fluid or blood showed it.⁵ PCT has been suggested to be an important early detection tool for infections because it is more specific and has a higher negative prediction value (NPV) than CRP.^{20,21}

A study by Farrokhpour et al. (2019) investigated inflammatory biomarkers such as changes in bloodstream PCT degrees and other inflammatory cytokines after bronchoscopy with BAL procedures. It found that 5.12% of individuals who had a fever after FOB. The percentage of positive culture results in serum culture was 2.56%, and the percentage of fever that lacked a specific cause was also 2.56%. PCT, IL-8, and IL-6 levels increased up significantly in individuals who had fevers.⁶ PCT concentrations above 0.5 ng/ml exhibit a sensitivity of 81% and a specificity of 84%. It is in contrast to the findings of Huang et al., that found no significant increase in IL-8 levels among healthy volunteers following bronchoscopy. The contradiction is caused by variations within the study population. The amount of 28 healthy individuals participated in the study so as to examine the natural consequences of bronchoscopy with BAL.⁵

Bronchoscopy with EBB is recommended for patients with lung cancer with the goal to determine the histopathologic diagnosis. For bleeding complications during bronchoscopy, several risk factors have been identified: thrombocytopenia, anticoagulant or antiplatelet therapy, immunosuppressed conditions, severe hepatic and renal impairment, mechanical ventilation practice, pulmonary arterial hypertension, and tendencies for bleeding. A large proportion of patients undergoing EBB procedures, on the other present, had no identified risk factors for hemorrhage associated with FOB. As a result, biological marker recommendations for predicting EBB-induced hemorrhage are necessary.⁶

Wang et al. (2019) present additional evidence that elevated serum CRP levels prior to treatment are an independent risk factor for hemorrhage during EBB in patients with lung cancer. The CRP degrees in the bleeding group were found to be substantially higher in this study than those in the non-bleeding group. The CRP threshold value in the hemorrhage subgroup was 1.15 mg/L, and Area Under Curve (AUC) of CRP was 0.692. Sensitivity was 94.04 percent, specificity was 31.2 percent, NPV value was 89.5 percent, and positive predictive value (PPV) was 89.5 percent for the CRP value. The clinician can use to determine which biopsy to conduct and the most effective way to manage bleeding during EBB with the support of these parameters.⁶

Lee et al. (2022) did a retrospective study to concurrently measure CRP, PCT, and IL-6 degrees in patients affected with bacterial infections. IL-6 increased first among patients with bacteremia, followed by PCT and CRP.²⁵ It is imperative to promptly and accurately identify

infections by finding suspicious clinical manifestations and analyzing relevant inflammatory biomarkers that contain clinical importance. Long-term kinetic profiles of patients with early infection or bacteremia derived from massive study databases show that IL-6 and PCT or CRP experience a significant increase in value within the first 24 hours, accordingly.²⁴

These findings additionally support the view that rapid IL-6 testing following hospitalization could be beneficial. In patients with a 30-day mortality rate, chronic elevation of IL-6 signifies a continuous inflammatory condition that helps in the evaluation of an unfavorable prognosis. Patients with an unfavorable prognosis continue to as there CRP levels rise, whereas those without mortality have stable CRP levels. Given the time spent between the patient's clinical presentation and the initial test, it is imperative to exercise caution when analyzing these data.^{24,25}

A more specific assessment of the presence and severity of inflammation or infection at the time of examination may be compromised by the variation in the kinetic properties of inflammatory markers subsequent to the initiation of pathophysiologic alterations (figure 5). For the accurate and timely assessment of the status of inflammation or infection, it is more beneficial to measure multiple inflammatory markers concurrently.²⁴ The comparison of CRP measured only once in special circumstance (e.g., to distinguish acute bacterial and viral infections and myocardial infarction) with periodic examination of CRP may provide a more accurate prognosis

of the inflammatory process through the inclusion of dynamic changes.^{23,25-28}

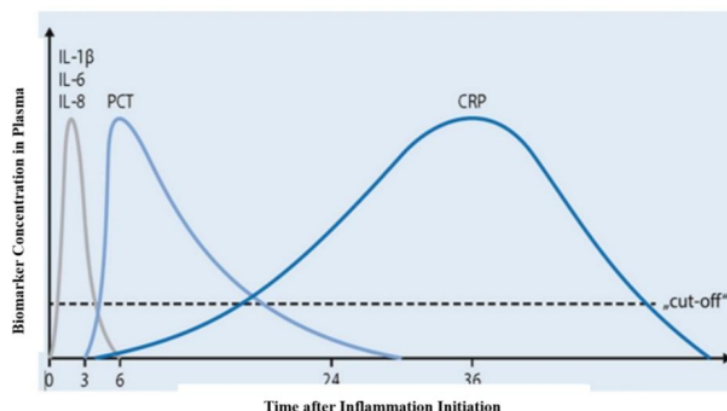


Figure 5. Timing of Inflammatory Biological Markers after Pathogen Exposure

CONCLUSION

Fever is a clinical manifestation that may be evaluated as a compensatory mechanism of homeostasis to the possibility of infectious complications after bronchoscopy procedures. The justification for contemplating prophylactic antibiotics prior to bronchoscopy procedures is the risk of sepsis from pneumonia caused by viral or bacterial contamination. However, this remain a contentious issue, including the potential for antibiotic resistance resulting from the use of antibiotics. Nevertheless, the evaluation of cultural outcomes is both time-consuming and costly.

Many studies have shown that CRP and PCT levels increase, fever whether or not, after bronchoscopic procedures. The increase in proinflammatory cytokines suggests the development of an infectious and inflammatory response after to the bronchoscopy procedure. From the basis of this analysis, PCT and CRP screening may be considered as replacement for routine screening during bronchoscopy procedures. It is advisable to perform an

biomarkers 24 hours after the bronchoscopy procedure with the aim to enhance the targeting and efficacy of prophylactic antibiotic administration. Probability of acute complications after bronchoscopy procedures may be established mainly through the utilization of CRP and PCR analysis, which detect bacterial infection.

Manuskrip CRP dan Procalcitonin.

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