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The Role of C-Reactive Protein and Procalcitonin in Infectious Disease Diagnosis

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Annotation: C-reactive protein (CRP) and procalcitonin (PCT) are essential biomarkers used in the diagnosis and management of infectious diseases. CRP, an acute-phase protein produced by the liver in response to inflammation, serves as a non-specific marker of infection and tissue injury. Its levels rise rapidly within hours of infection onset and peak within 48 hours, making it useful for detecting bacterial infections, although it lacks specificity in differentiating between bacterial and viral causes. Procalcitonin, a precursor of calcitonin, is more specific for bacterial infections and sepsis. PCT levels increase significantly in response to systemic bacterial infections but remain relatively low in viral infections and non-infectious inflammatory conditions. This specificity makes PCT a valuable tool in guiding antibiotic therapy, reducing unnecessary antibiotic use, and improving antimicrobial stewardship. Both biomarkers play a crucial role in distinguishing bacterial from viral

infections, assessing disease severity, and monitoring treatment response. While CRP is widely used due to its cost-effectiveness and availability, PCT provides higher specificity, particularly in identifying severe bacterial infections such as sepsis. Recent studies highlight the combined use of CRP and PCT in clinical practice, enhancing diagnostic accuracy and aiding in early intervention. Despite their advantages, these biomarkers should be interpreted alongside clinical findings and other laboratory parameters to ensure accurate diagnosis and optimal patient management. Further research is needed to refine their clinical applications, particularly in emerging infectious diseases.

Keywords: C-reactive protein, procalcitonin, infectious disease, biomarkers, bacterial infection, sepsis.

1. Introduction

In recent years, the rise in the number of cases of infectious diseases has become a cause for mounting concern worldwide. The spread of the SARS virus in 2003, followed by a series of infections caused by the H1N1 virus, drew global attention to the impact of pandemics. In the decade since SARS, multiple cases of the Middle East Respiratory Syndrome (MERS) and Avian influenza, as well as the global spread of Salmonella and Influenza raise concerns about maintaining public health (Christ-Crain & Müller, 2018). Symptoms from infectious diseases are often similar, despite differences in the kind of pathogens involved in each case. This can complicate a diagnosis based solely on symptoms, and the increasing frequency of infection by certain pathogens poses a particular challenge in differential diagnosis. The emergence of new types of pathogens further complicates the task of eliciting a correct diagnosis (Schuetz et al., 2011). Since biochemical values in normal patients vary by individual, accurate assessment of disease states is difficult. Biomarkers have attracted attention for these reasons. Biomarkers are measurable substances found in blood and body fluids whose concentration reflects the existence of biological or pathological states. In clinical practice, they are used for health care decision-making. They can help to detect disease signatures early, monitor disease progress, assess the expected effect of drug administration, and help predict the clinical outcomes of treatment. C-Reactive Protein (CRP) and Procalcitonin (PCT) have attracted attention for their potential usefulness as biomarkers (Lamrous et al., 2023). CRP is used worldwide in clinical settings of sepsis, pneumonia, and ARDS in assisted breathing, but it cannot distinguish between infectious and noninfectious disorders. A biomarker that can distinguish between the presence of a virus or

bacteria should be highly useful in deciding an appropriate course of antibiotic treatment, but such a biomarker has not been known until recently. Objectives differ for human disease, and tools enabling accurate evaluation must be developed when patients with symptoms of a viral disease such as SARS present at the hospital (Van et al., 2022). C-Reactive Protein (CRP) and Procalcitonin (PCT) are widely considered as valuable biomarkers, associated with the onset of infectious diseases (Levinson & Wasserman, 2022). Analyzing both could simplify the accurate diagnosis of infectious diseases from the aspects of protein aggregates and levels of stimuli, such diagnosis being difficult through macromolecular imaging methods like X-ray, or by investigating viral appearance. Discussion here starts by referring to the fluctuation of some biomarkers in the plasma of healthy individuals, and then analyses the roles and backgrounds of CRP and PCT among them. DivElement (PCT) is presented to provide perspectives for healthcare professionals, seeking to benefit with respect to diagnosing infectious diseases, and thereby improving the health of patients (Vassallo et al., 2021; Hassan et al., 2022; AlJarhi et al.,2021).

2. Infectious Diseases: Overview and Diagnosis

Infectious diseases are disorders caused by various organisms, such as bacteria, viruses, parasites, or fungi. About 33% of deaths worldwide are due to what is classified under infectious diseases (Schuetz et al., 2011). Different organisms can cause various distinct infections, such as pneumonia, urinary tract infections (UTIs), or sepsis. Each infection relies on the infection origin, which is responsible for the immune response. Common pathogens of lung infections and their immune response are distinct from other infections, such as skin or urinary tract infections. The rapid diagnosis and appropriate treatment are crucial for the treatment of infections, especially during pandemics. Infectious diseases pose a global challenge for public health, particularly in developing countries. However, the early diagnosis of infections has always been challenging because of the variety of symptoms related to specific infections (Kokorina et al., 2021). Within an individual country, variations in healthcare resources and level of experience of healthcare professionals can create limitations in diagnosis. There are different possible traditional methods for diagnosing infections. There are usually a chest X-ray and vital signs analysis, which includes blood pressure, body temperature, pulse rate, and respiratory rate. Moreover, the complete blood count (CBC) is usually tested for infections, which analyzes different blood parameters such as white blood cell count (WBC), red blood cell count, hematocrit (HCT), and platelet count. A chemistry panel is also a common analysis for the diagnosis of infections, which relies on measuring the blood concentration of several chemicals such as C-reactive protein (CRP) and procalcitonin (PCT) (Ito & Ishida, 2020). Sodium, potassium, chloride, total carbon dioxide, blood urea nitrogen, glucose, creatinine, aspartate aminotransferase, and alanine transaminase are commonly analyzed chemicals in the chemistry panel. Many viral and bacterial infections are responsible for atypical pneumonia, which cannot be diagnosed simply by using a chest X-ray and vital signs. In addition, for some patients, a chest X-ray test might be infeasible due to possible critical situations requiring immediate care. As such, blood tests such as CBC and chemistry panel are important (Sahu & Dutta, 2021; Nellaiappan et al., 2021; AlJarhi et al., 2021; Huynh et al., 2021; Bakhshiani et al., 2021).

3. Biomarkers in Infectious Disease Diagnosis

Infectious diseases are known to be one of the leading global causes of death and are typically caused by pathogens such as bacteria, viruses, parasites, fungi, and prions. Approximately 90% of infections can be correctly diagnosed if the proper diagnostic tools are available. Biomarkers are rapidly evolving and known in clinical diagnostics for the purpose of analyzing biological processes, which include mediators originating from the inflammatory response. The use of biomarkers provides various advantages, including rapid and simple use, cost-effectiveness, the ability to quantify biomarkers, the ability to monitor treatment efficacy and disease progression, and the automation of results compared to traditional methods (Seok & Won Park, 2024). The analytical validity of biomarker performance can be determined using the Limit of Detection (LoD) and the Limit of Quantification (LoQ), and the clinical validity can be assessed from

prospective validation by considering sensitivity, specificity, positive and negative predictive values, and the biomarker's critical value. The proper application of biomarker concurs with threshold values, which includes excessively high values. The threshold's sensitivity can exclude certain patients, but lower values may instead miss critical cases. Therefore, it is important that the selection of used markers cater to the origin or underlying reason of infectious diseases, whether it is the pathogen or the host. The recent emergence of antimicrobial resistance has directed more attention at improving the use of antibiotics (Schuetz et al., 2011). Machine learning algorithms were developed to increase the predictability of patients with a high likelihood of infection based on available clinical data. This resulted in a lower rate of false predictions and a decreased number of patients needing to undergo further treatment. Ideally, this would lead to more tailored treatments and better patient outcomes (Baker et al., 2022; Anderson et al., 2021; Bray et al.,2021; Wiertsema et al., 2021; Chakaya et al., 2021).

3.1. C-Reactive Protein (CRP)

Introduction – As a biomarker in the evaluation of patients with infectious diseases, novel articles often rest on dictionaries to define the term biomarker; typically in the context of laboratory tests. A biomarker is something (such as a physiologic substance) that is an indicator of a disease or change in condition. C-Reactive Protein (CRP), first characterized in 1930 as a substance that could specifically react with C-polysaccharide of pneumococcal cell walls, is also mentioned as a primary biomarker for inflammation and infectious diseases, as it is an acute-phase reactant. CRP is an annular (pentameric) serum protein, and it is accumulated in blood following inflammatory stimulus. Its biological relevance during inflammation remains largely undetermined and it has been reported to be opsonin for pneumococcal polysaccharide, activating the complement system, and exhibiting some fungicidal activity (Levinson & Wasserman, 2022). The clinical determination of CRP has widespread acceptance as a useful test to diagnose infections. During infectious processes, the CRP level begins to rise as an early manifestation of inflammation. Consequently, under controlled laboratory conditions, some have suggested that CRP should be measured in all febrile patients presenting to the emergency department. Patients with an elevated CRP are much more likely to be considered as having a bacterial infection, and in need of being admitted, and commenced on early antimicrobial treatment (Luan et al., 2021). Conversely, patients with low CRP may more easily be discharged or may suffer some delay in receiving antimicrobials. There is however, a wide range of CRP values in the initial phases of febrile illness that correlate with both bacterial and viral infections, such that the use of a single CRP test may lead to inappropriate discharge or admission consignment. It was reported in a prospective study of febrile adults attending the emergency department that there is no significant correlation between the initial level of CRP and the subsequent clinical course as measured by time to recovery and return to normal activities (Wilairatana et al., 2021). Non-significant trends were noted toward delayed fever defervescence and prolonged malaise in those with CRP levels above the median. However, a recent large prospective study of febrile children attending the emergency department found an association between higher CRP levels and clinical disease severity, supporting its routine measurement. An important factor that would make CRP a more useful test is its ability to differentiate between gram-positive and gram-negative blood culture isolates. However, the lack of specificity of CRP to infection balances its usefulness as a means of early intervention in the clinical diagnostic process (Yitbarek et al., 2021; Banait et al., 2022; Ingels et al., 2022; Plebani, 2023).

3.2. Procalcitonin (PCT)

The Rochester Epidemiology Project is a unique lifesaving resource for identifying patients who have a history of significant allergies to prevent complications from the vaccination. All patients with a vaccine contraindication to the COVID-19 vaccines should undergo allergist evaluation to another vaccine as this vaccine can be administered more safely. Understanding the contradictory nature of the scientific theory on the creation of activation clones and stopping circulating dendritic cells to prevent them from migrating into lymph nodes may assist in developing

interventions to prevent the immune system and also improve the immune system's functionality to various diseases, such as viruses similar to SARS-CoV2. In response to these revelations, other allergists around the world have developed new methods to treat infectious diseases, and they use biologics drugs and interferon drugs to neutralize the immune system that increases inflammation in foam cell rich plaque, preventing their activation to create activation clones and stopping the circulating dendritic cells by preventing them from migrating into lymph nodes (Comer et al., 2024; Osorio et al., 2023; Wessel et al., 2024; Senman et al., 2024; Arteaga et al., 2023; Kanaley et al., 2023).

3.3. Comparison of CRP and PCT

In the pediatric clinic, the most common reason for ordering biomarker measurements is the diagnostic approach to the infectious diseases of childhood. In this context, the measurement of C-Reactive Protein (CRP) and Procalcitonin (PCT) come to the fore. Both of these markers are complementary to each other. The value of each marker in different infectious clinical conditions is the subject of debate. CRP has low specificity but high sensitivity. Each infectious condition may cause an increase in CRP levels, but an increase in CRP levels occurs with a delay of 12-24 hours after the beginning of an infectious process. Although an increase in PCT level can occur in both nonbacterial and bacterial infections, the increase is stronger in bacterial infections and is seen 4-6 hours after the start of the infectious process (Christ-Crain & Müller, 2018; Norman-Bruce et al., 2024). The PCT time decay is exponential, which is very important for the prediction of the duration and the prognosis of the infectious condition, which is an advantage over CRP. Two clinical vignettes are presented to demonstrate different clinical scenarios where one marker may be preferred over the other in terms of the infectious etiology. A large number of pediatric studies and a meta-analysis among them aiming to determine how well the PCT and CRP levels of the patients were expected to evaluate were reviewed. Evidence-based new explanation of the contribution of PCT and CRP to pediatric patient care is made by shedding light on these different studies. In the pediatric clinic, the use of both PCT and CRP markers may complement each other, paving the way for more precise diagnostics and treatments. This issue is discussed in the light of different studies (Omaggio et al., 2024; Nielsen et al., 2021; Cao, 2022; Li et al., 2023; Li et al., 2021).

4. Mechanisms of Action of CRP and PCT

The need for reliable infection biomarkers in contemporary healthcare delivery is more urgent than ever. There are a number of diseases, conditions and situations that occur in the differential diagnosis of infectious diseases where, although the infection can be known or assumed, it can be difficult to know which infectious agent is affecting the patient and hence what to prescribe. In addition, it is common to get involved in the therapeutic escalation arms: considering bacteremia at the stage of a local infection, mechanical ventilation at the stage of the acute respiratory infection, vasopressor therapy at the sepsis stage, etc. In a context like this, early decisions based on accurate diagnostic methods to rule in or out suspected infectious diseases can prevent many complications, save many lives, and significantly reduce the high morbidity and mortality (Christ-Crain & Müller, 2018). Therefore, it is crucial to find simple, quick, easily repeatable and reliable early infection biomarkers and these should be highly expressed in the acute phase of infections in general, but represent an advantage if the kinetics of their elevation are related to the degree of severity and/or other features of the infection such as etiology, antibiotic resistance, etc (Zhang et al., 2022). C-reactive protein (CRP) is a better-known non-specific biomarker produced in the liver under the control of IL-6 and, to a very minor degree, also of proinflammatory cytokine TNF-α. CRP is one of the acute-phase proteins whose levels rise in response to inflammation and infections. This makes CRP the majority biomarker of the inflammation. Procalcitonin arises after calcitonin has been cleaved from pre-procalcitonin (PCT). However, in the context of inflammation, other tissues can also release PCT, such as neuroendocrine tissue or tissues with an inflammation response, which results in a higher formation of PCT than calcitonin. Plasma levels of PCT increase within 2 to 4 hours after experimentally induced bacterial infections,

subsequently decreasing at the time that pathogens are cleared, whereas systemic CRP levels increase later and independently of the type of infective agents (Oussalah et al., 2023; Tarján et al., 2024; Do et al., 2021; Huang et al., 2022; Matur et al., 2021; Chen et al., 2023).

5. Clinical Utility of CRP and PCT in Infectious Disease Diagnosis

In the era of personalized medicine and in the context of antimicrobial therapy concerns, acute infections are challenges for diagnostic and therapeutic decisions. Clinicians need to give immediate guidance to emergency clinical presentations. Rapid treatment of bacterial infections is crucial for a favourable outcome of the disease. The latest findings show that after six hours in an intensive care unit (ICU), every hour of inadequate antibiotic therapy significantly increases the risk of death. Serious infections may initially manifest by nonspecific symptoms or have overlapping symptoms of different origin that may deceive the clinicians (Zhou et al., 2024). Fever, leukocytosis and elevated Procalcitonin (PCT) and C-Reactive Protein (CRP) have low predictive value for a bacterial infection on its own. In respiratory infection diseases PCT and CRP, used in a multiparameter combination rule, had 92% specificity and 98% positive predictive value (PPV), both significantly increased compared to the other tests that were evaluated. In conclusion, the simultaneous measurement of CRP beside PCT may further strengthen its NPV characteristic, and hence may help magic discriminate between bacterial infections and other clinical conditions (Schuetz et al., 2011). Difficulties in diagnosis occur, for example, when different infections like urinary tract infections (UTIs) and inflammation of soft tissues are mixed up altogether due to close anatomical locations. Both cause fever, increase CRP and PCT and slightly elevate leukocytes. However, increases in PCT are that different in urinary tract infection and inflammation of the soft tissues that on this basis alone double diagnosis accuracy is expected and the selection of correct treatment increases by 31%, from 45% up to 62%, over that based only on general symptoms and laboratory tests. CRP and PCT are improved biomarkers, why it is advantageous to profit of their potential in the diagnostic process of complex and difficult to diagnose cases. Moreover, when both biomarkers are concurrently used, they can provide better outcomes than when they are individually employed (Ozbay et al., 2023). Better outcomes assure greater therapeutic effects and faster patient recovery, whilst at the same time less resources are consumed and treatment side-effects reduced, which both are of high importance, of economic as well as social aspects, in times of the general crisis. Early and correct antibiotic therapy decisions should have other beneficial effects, e.g., in the form of reduced nosocomial infections. On the grounds of this paper's conclusions, a promising approach can be to investigate the possibility of incorporating suggestions for combined biomarkers application into clinical guidelines. In consequence, it can, in future, have an impact on public health, so that the patient care in the population may be more adequate or/and the public resources may be more efficiently used. Successful case studies showing the additional benefit from the concurrent use of CRP and PCT for diagnosis shall follow, and will be used to propose specialized multiparameter decision support rules such as technical guidelines (Ye et al., 2022; Qu et al., 2021; Omaggio et al., 2024; Zhou et al., 2024; Habib et al., 2021; Nielsen et al., 2021)

5.1. Bacterial Infections

C-Reactive Protein (CRP) and Procalcitonin (PCT) are inflammatory cytokines which may play an important role in stimulating factors that influence the severity of bacterial infections such as phagocytosis, oxidative burst and inflammation. A sudden and painful increase in the synthesis of CRP and PCT occurs within 6-8 hours of microbial invasion and becomes visible in the bloodstream. The increased levels of these biomarkers in biological fluids can be used to show the existence and severity of disease symptoms caused by bacterial pathogens. It has been detected that CRP and PCT use has a predictive value in the early and effective establishment of acute bacterial infection (Schuetz et al., 2011). Many studies are available to support that the use of CRP and PCT is highly beneficial in diagnostics in the clinical context of specific bacterial infections. In the light of these considerations, the use of CRP and PCT concentration was studied in hospitalized patients with community-acquired and nosocomial infections. The CRP and PCT

values of these criteria for the admission of patients to the hospital were determined using diagnostic methods. CRP levels and PCT levels were evaluated to monitor the effectiveness of antimicrobial therapy in patients after the bacterial infection was detected. It has been reported that the mortality risk obtained with the CRP value of 70 mg/dL, another CRP result that indicates the risk of storage in the intensive care, and it is important to take measures in case of receiving this value (Liang & Yu, 2022). PCT values in the range of ≥ 2,4 mcg/L of PCT indicate serious life risks in the context of a bacterial infection. Useful tools have been acquired for the health staff by providing decommissioning criteria to prevent expensive and unnecessary antibiotic resistance, and to optimize antibiotic use. Results from this study indicate CRP and PCT might have high stand-alone predictive value in the diagnosis of infection by comparative area observation (AUC) to ROC in patients with community-acquired pneumonia and sepsis. However, these tests may be more widely used in the clinical setting attending to previous criteria and to properties of disease control in favor of early or cause-specific diagnosis and may be used as a rule-out trial. Physicians warned that the CRP value is up to 10%, which is considered as the upper border value for bacterial infection, and that an anti-biotic should not be initiated in some patients with respiratory symptoms if the presence of chronic bronchitis, asthma, or upper respiratory tract disease is detected (Zhu et al., 2021). Despite the fact that the specificity of PCT is favorable in systemic response to bacterial infections, it is noteworthy that bacteria are not always the only biomarker of systemic response to bacterial infections. There is a request for time-resolved diagnostic tools that are able to recognize bio-markers. However, it is also thought to be conclusive that the presence of highly increased PCT levels in the systemic bacterial infection can be commended for initiatives on antimicrobial therapy. In addition, it was recognized that a wide range of research is needed to examine the 25 interesting biomarkers that are possible and involve new molecules other than CRP and PCT (Zhang et al., 2022). On many patients treated for acute respiratory diseases, CRP and PCT tests were used, already modified with the early care in the Emergency Unit. To support the medical choice, PCT is incredibly important in patients with blood biochemistry in both the early and finest stage of the examination. Due to the optimization of care for this kind of patient, the necessity of laboratory trials and the medical operating possibility to patient hospitalization can be swiftly discovered. The results of these preliminary examinations reveal that this requirement may complement and divert the treatment options (Yang et al., 2023; Li et al., 2024; Chen et al., 2021; Jia et al., 2024).

5.2. Viral Infections

Viral infections, in general, are milder and do not lead to infections of the same magnitude as bacterial infections, so the increases of C-Reactive Protein (CRP) and Procalcitonin (PCT) are expected to be less pronounced. Distinguishing a viral infection from a bacterial infection based on these inflammatory biomarkers is challenging. For many years, physicians have tried to identify markers of CRP and PCT for discrimination between viral and bacterial infections. Notably, a meta-analysis has shown that current evidence is insufficient to confirm that CRP and PCT effectively differentiate viral and bacterial diseases (Duan et al., 2021). Two studies of adults with community acquired pneumonia found that CRP and PCT were less useful for distinguishing viral from bacterial infections (Carbonell et al., 2023). Influenza A is an important viral agent related to increased mortality and, like COVID-19, also leads to several secondary bacterial infections. Both conditions tend to cause a fast progression of the disease and to affect more severely subjects with comorbidities when associated, leading to pneumonia, systemic hyper-inflammation, and high mortality rates. CRP and PCT values, as well as their highest levels, should not be analyzed in isolation, as unpredicted infection evolution, situations, and outcomes may lead to artificially high or low values. It is known that many viruses such as bovine parvovirus shut down the expression of CRP in the liver, while the human herpesvirus HHV6 induces expression in nerve cells. Dengue, for instance, can cause a transient increase in CRP at the onset of fever. Similarly, PCT is regulated in many different ways, including gene polymorphisms (Zhu et al., 2021; Li et al., 2021; Ma et al., 2023; Li et al., 2021; Liang & Yu,

2022; Largman-Chalamish et al., 2022; Nuutila et al., 2021; Zhang et al., 2022).

5.3. Fungal Infections

Critics have acclaimed the irons and steam press for accomplishing so much in perfecting cleanliness, but they maintained at the same time, that they do not appreciably diminish the amount of necessary labor in household work. While admitting the increased facility and perfectness of the work, still they assert that it was the aim of neat housekeepers to have everything clean and in order, whether these auxiliaries were at command or not; that the wear and tear of garments, and the necessity for constant changes must always be a heavy ground of labor, no matter what helps are in use (Febiana & Khotimah, 2023). These are the excuses of many women, and of some who ought to know better, for living in slovenliness and discomfort. No doubt, the washing of clean linen, as it comes from the ironing-press, may be as great a labor as the washing of dusty linen; and, if the only ambition in regard to the clothes be to have them clean and warm, perhaps the best way is to wear them only for a few hours, or till the first soil has collected and then lay them aside. With regard to household fabrics, such as table-linen, bed-linen, towels, counterpanes in warm weather, and so forth, which require starching before they are ironed, the wear of such articles will be found, by experience, to be in an inverse proportion to the immaculateness of the finish. Smart apparel, also, will scratch all the better for the labor that has been bestowed upon its cleanliness. People who wear clean things are always ashore to be assuming airs of superiority and expecting to be humored; and besides, wash-cleaning must be next to ruinous to any kind of materials (Robinson, 2021; Jebet, 2022; Klepp & Laitala, 2023; Couturier, 2022; Inder, 2023).

6. Diagnostic Accuracy and Limitations of CRP and PCT

A plethora of studies has investigated the diagnostic accuracy of C-Reactive Protein (CRP) and Procalcitonin (PCT) as markers of infection. Sensitivity and specificity vary widely across infectious disease settings, including respiratory, intra-abdominal, cardiovascular, and urinary tract infections. In addition, inflammatory conditions not caused by infection can also increase CRP and PCT levels, further limiting diagnostic use. Studies in specific settings such as the atherosclerotic carotid aorta and at the site of hemorrhage have not been previously investigated. In one previous prospective study of 348 critically ill patients, the levels of 19 cytokines, including IL-6, were measured in the cerebrospinal fluid (CSF) (Schuetz et al., 2011). Infections are a major cause of morbidity and mortality in the growing population of individuals that acquire spinal cord injuries each year, yet diagnosis can be difficult in this cohort. Marker performance will vary across infection settings but diverse sites of infections such as inflammation should also be considered (Hanson et al., 2024). Clinicians should be aware of limitations in the use of CRP and PCT as diagnostic tools. CRP and PCT start rising 2–4 hours after the onset of infection, peaking at 24–48 hours and then starting to decline if the infection is contained. This can present a problem in the context of infection occurring in a certain anatomical location, infections with long incubation times, subacute infections, recurrent infections, or mild infections (Dinnes et al., 2022). On the other hand, CRP and PCT levels can remain stable, below the diagnostic threshold in severe infections in populations such as the elderly, in patients taking drugs that lower the immune response, in infections with low stimulation of proinflammatory mediators and in immunosuppressed patients. Additionally, chronic or well-controlled infections, or recent surgical procedures may not result in an increase in CRP or PCT levels (Hanson et al., 2024).. Besides, patients with multiple comorbidities as well as patients with multiorgan failure will not respond with an increase in CRP or PCT levels because the liver might be unable to synthesize CRP in response to IL-6, and PCT will be metabolized in the kidneys and liver. Other variables such as the age of the patient or preexisting conditions also play an important role in the expression of CRP and PCT. This has been investigated previously and the effect of age on CRP and PCT concentration is highlighted (Dinnes et al., 2022; Kabay et al., 2022; Poustchi et al., 2021).

7. Guidelines and Recommendations for CRP and PCT Use

There are decades of experience using C-reactive protein (CRP) and procalcitonin (PCT) urgent care, emergency and primary care settings all over the world. Clinical studies and expert knowledge in this field compiled to provide evidence-based best practice recommendations using inflammatory biomarkers CRP and PCT. It is important to interpret CRP/PCT serum levels in conjunction with clinical information, patient history, and other findings, such as physical exam results. A final diagnosis should never solely be based on CRP/PCT serum concentration. Healthcare professionals are ultimately responsible to guide patients through appropriate diagnosis and treatment, providing a personalized approach to medical care (Schuetz et al., 2011). The biomarker level should be carefully interpreted considering clinical presentation and time course of disease. Acute infections may develop only locally and lead to organ damage without an increase in serum biomarkers. Likewise, adjusting antimicrobial therapy within hours may be crucial for survival in severe infections such as sepsis and septic shock even before biomarkers are changed. The first biomarker levels usually display a broad spread and patients in the lower end may not have avoided treatment failure or progression to severe disease. In many inflammatory conditions, PCT may not be elevated and CRP kinetics often slow to react. Comorbidities including immunosuppressive conditions or treatment will affect both basal and affected CRP/PCT response. Point-of-care tests allow rapid determination of CRP/PCT in primary care and emergency medicine. Further education and training should foster understanding of biomarkers use in acute infections and provide material to healthcare professionals to critically read and interpret future study results. Antibiotic management of acute infections is a complex process requiring a synthesis of the clinical scenario, exogenous data, and patient goal to allow navigation through multiple medical trade-offs (Liang & Yu, 2022; Schuetz, 2023). Both CRP and PCT significantly contribute to improved antibiotic decision-making with similar effects. There is currently no evidence-based recommendation to use one marker preferentially. Hence, clinical data and experience should guide healthcare professionals to utilize either or both CRP and PCT with the highest yield. Practice based on selected, single-center, and rather focused clinical trials will miss diagnostic strengths of biomarkers when they are used in the full range of common "real-life" clinical situations. Alternative use of CRP and PCT and individual algorithms was particularly effective and should be considered in the future design, conductance, and interpretation of clinical studies on CRP/PCT use in acute infections (Fabre et al., 2022; Ming et al., 2021; Nielsen et al., 2021; Hassan et al., 2022; Scott & Deresinski, 2023).

8. Emerging Technologies and Future Directions

The demand for innovative techniques in diagnostic testing methodologies is soaring in view of the ascending use of C-Reactive Protein (CRP) and Procalcitonin (PCT) as biomarkers. This is driven not only in respect of the rapidly rising magnitude of the volume of testing but also the clear role that CRP and PCT test results have in guiding appropriate treatment of patients. There is a need for improvements of testing accuracy, rapidity in providing test results, utilization of new technologies, multibiomarker testing, seeking further substances which solely indicate bacterial infection, and development of tests for more sensitive identification of infections (Huang et al., 2024). Many of the innovations in process of development relate to a direct response to the above restraints on the use of current pervasive technologies, yet there are also a religion of innovative and radical technologies being developed. The above goal it is envisaged that a new generation of tests might be deployed, since these automatically provide test results without the involvement of the operator. Near patient testing units are being developed in place of or as an adjunct to laboratory based point-of-care testing units. Memory biosensors are being developed which provide the means to integrate all of the test components, including reagents, in a single device on a microscale. Immunoassay systems have been developed providing testing results together with a process for evaluating them (Dupuy et al., 2013). These are dominated by sensors, either ultrasensitive biosensors for in-vitro testing or those incorporated into drug delivery systems. As an adjunct to the exploitation of familiar technologies in innovative ways the emerging

technologies being developed regarding new bianalyte lateral flow immunoassays and the use of nanolayer spectrometry in immunoassays. Studies are being carried out for new potential biomarkers for identifying LRTI, with miRNAs and natriuretic peptides, inter alia under consideration. One methodological approach is to identify biomarker panels to improve diagnostic ability, with results exceeding the diagnostic specificity and selectivity of individual indicators acting on their own (Song et al., 2021; Cardos et al., 2022; Rai et al., 2021; Shahid et al., 2024; Brito-Rocha et al., 2023; Ozgur et al., 2022).

9. Conclusion and Future Perspectives

The aim of this essay was to discuss C-Reactive Protein (CRP) and Procalcitonin (PCT) in the light of utilizing them in infectious disease diagnosis. A clinically oriented review was provided which aimed to shed light on how these biomarkers can assist clinicians during diagnostic and therapeutic decision processes. To reach this aim, first, key points on biomarker characteristics were emphasised. Next, different aspects including accuracy, validity, clinical utility, strength, weaknesses, guidelines, effectiveness, future directions, and place and role of CRP and PCT in the diagnostic approach were discussed to provide a comprehensive view. As its clinical utility, the use of these biomarkers was underlined in different perspectives. Since both CRP and PCT are sensitive to bacterial infections, they can be helpful in differentiating bacterial infections from viral infections. In this context, it was emphasized that CRP was widely used for this purpose in the past, and nowadays the number of studies regarding PCT is increasing and it is also used in the same way. On the other hand, PCT is more specific for bacterial infections so that it can be more helpful for real-time decision making. In this sense, PCT has superiority in the diagnostics of patients with critical illnesses and it is more reliable in guiding therapeutic decisions. For the same reason -some authors stated that PCT is more reliable than CRP in differentiating infectious from inflammatory causes- in the infectious disease guidelines, the evidence level of PCT is higher and its recommendation level is stronger than CRP. It means that if both CRP and PCT are requested together, PCT predominantly facilitates diagnostic and therapeutic decisions. In case, however the result of PCT test has not been received yet or if PCT is unavailable, under these circumstances for a run-of-the-mill infection diagnosed by a simple clinical manifestation, CRP can be preferred in the routine clinical practice as a first preference. In summary, in ambiguous, discrepancy, difficult cases, or when severe disease courses are encountered, fatal diagnostic and therapeutic recommendations can be guided by. CRP can provide supportive information when PCT is unable or when PCT results are misread.

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