

## Review Article

# Host biomarkers for early diagnosis of infectious diseases: A comprehensive review

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## Abstract

Biomarkers have been used in the diagnosis of disease and other conditions for many decades. There are diverse ranges of analytical targets, including metabolites, nucleic acids and proteins were used as a biomarker. Clinical diagnoses already rely heavily on these for patient disease classification, management, and informing treatment and care pathways. For that there is always a need of rapid and point of care test. However, until fairly recently, studies of biomarker efficacy in a clinical setting were mainly limited to single or dual use, and the landscape was complex, confused, and often inconsistent. Few candidates emerged from this somewhat clouded picture: C-reactive protein, procalcitonin (PCT) for sepsis, ADA for mycobacterium tuberculosis and a Circulating miRNAs serve as molecular markers for diverse physiological and pathological conditions.

## Introduction

Effective biomarker are utmost important for the early diagnosis of various diseases. Biomarkers have been used in the diagnosis of diseases and other conditions for many decades and include a diverse range of analytical targets. All over the world acute febrile illness is a common presentation in any primary care settings [1,2]. Although there are infective and non-infective causes for febrile illness, the most common causes of AFI in India are dengue and malaria. Other than AFI the diagnosis of tuberculosis (TB) continues to be a challenge in clinical practices [3]. Routine diagnostic methods are very useful but do not provide enough sensitivity and specificity. For many decades diverse range of analytical targets such as metabolites, nucleic acids, proteins were used as biomarkers [4]. Out of many tested biomarker CRP, procalcitonin and adenosine deaminase were emerged a potential biomarker for point of care platforms. Clinical diagnoses already rely heavily on these for patient disease classification, management and informing treatment and care pathways [1].

In recent year there are different new biomarker known as miRNA and IP-10 which are widely studied to know the potential of disease diagnosis. The primary objective of this comprehensive review was to summarize the role of host biomarkers in diagnosis of infectious diseases.

## Methods

### Literature survey

A literature search of Medline, PubMed, and Google Scholar was done using the term

“biomarker, detection of biomarker, role of biomarker in diseases diagnosis, miRNA. On the basis of title and displayed abstract, articles were chosen for the selected topics. Among the non-English articles, only those with abstract in English were reviewed and included. Of the published articles, 38 original articles and 12 reviewed were excluded in which studies were mainly focused on role of biomarker in infectious diseases diagnosis.

### C-reactive protein

CRP, named for its capacity to precipitate the somatic C-polysaccharide of *Streptococcus pneumoniae*, was the first acute-phase protein to be described and is an intricately sensitive systemic marker of inflammation and tissue damage [5]. CRP is synthesized primarily in liver hepatocytes but also by smooth muscle cells, macrophages, endothelial cells, lymphocytes, and adipocytes. C-reactive protein exhibits elevated expression during inflammatory conditions such as rheumatoid arthritis, some cardiovascular diseases, and infection [6]. In healthy young adult volunteer blood donors, the median concentration of CRP is 0.8 mg/l, the 90<sup>th</sup> centile is 3.0 mg/l, and the 99<sup>th</sup> centile is 10 mg/l, but, following an acute-phase stimulus, values may increase from less than 50 mg/l to more than 500 mg/l, that is, 10,000-fold [7]. CRP was the most frequently studied host biomarker in this review and the majority of these studies (33/36; 92%) reported statistically significant differences in CRP levels measured in patients with bacterial and those with non-bacterial infections. Half of the studies (18/36; 47%) reported sensitivity and specificity at ranges of 61.2%-100% and 26%-100% respectively to identify bacterial infections [3,8-10]. All studies comparing CRP levels in blood specimen of patients with meningitis (5/5) reported statistically significant differences in CRP levels between the bacterial and viral group, with higher levels seen in bacterial infections [11-13]. yet an another study investigators examined CRP in bacterial and fungal sepsis within a neonatal intensive care population in Turkey and found that CRP levels were lower in bacterial sepsis patients (mean 11.4 mg/l) than in fungal sepsis patients (mean 28.0 mg/l,  $p = 0.026$ ) [14]. However, they did not report diagnostic performance characteristics. A study in Malawian children found significantly higher CRP levels in bacterial infections compared to patients with viral causes (median 185.4 vs. 18.3 mg/l,  $p < 0.001$ ) [10]. However, in children with malaria, CRP levels were not significantly higher during bacterial than viral pneumonia (median 217.4 vs. 96.8 mg/l,  $p = 0.052$ ), indicating that CRP might be valuable as a diagnostic only after malaria has been ruled out [3].

### Procalcitonin

Procalcitonin (PCT) is used as a biomarker for the diagnosis of bacterial infection such as sepsis and septic shock [15]. PCT is produced ubiquitously in response to endotoxin or mediators released in response to bacterial infection (IL-1 $\beta$ , TNF and IL-6) and strongly correlates with extent and severity of bacterial infections, it also helpful to distinguish bacterial infections from viral illnesses [16,17]. For the diseases diagnosis and prognosis PCT shows a favorable kinetic profile for use as a clinical marker: it promptly increase within 6 to 12 hours upon stimulation and circulating PCT levels halve daily when the infection is controlled by the host immune system or antibiotic therapy [18]. PCT correlates with bacterial load and severity of infection [19,20].

At present there are no gold standard exist for the detection of blood stream infection as the chances of contamination is very high with coagulase negative staphylococci while collecting the blood sample. At this point PCT demonstrated a batter role for the diagnosis of sepsis in compare to WBC and CRP. In a study researcher had observed that a cut off of 0.1ug/L, PCT had a very high sensitivity to exclude true infection [19,21]. Yet in another study by Muller et al., observed that PCT cut off of 0.25ug/l was most helpful to exclude bacteremia [22].

For upper and lower respiratory tract infection in ICU patients with sepsis and post-operative infections, many studies have shown the effectiveness of using PCT algorithms to guide antibiotic choices [23,24]. So, PCT levels should be always evaluated in the context of a careful clinical and microbiological assessment. As the kinetics of PCT are of particular diagnostic and prognostic interest, repeated measurements should be performed if possible, especially in seriously ill patients if antibiotics are withheld. The limitations of every PCT measurement include false-positive and false-negative results [25]. Unspecific elevations of PCT levels in the absence of a bacterial infection can usually be seen in situations of massive cell death, for example after severe trauma or surgery [17,26,27]. In these situations, PCT values are usually only moderately elevated and show a rapid decline in follow-up measurements. On the other hand, falsely low PCT levels typically seen during the early course or localized state of an infection, often show an increase in the follow-up measurements. Thus, highly sensitive PCT assays are required, as subtle changes of PCT at very low concentrations can be monitored, increasing the sensitivity of the test and thus the safety of patients.

### Adenosine deaminase (ADA)

ADA is an enzyme catalyzing the deamination reaction from adenosine to inosine. It is also an essential enzyme of the purine catabolic pathway [28]. ADA acts in proliferation and differentiation of lymphocyte, especially T lymphocyte. It also acts in maturation of monocytes transforming them to macrophage. ADA is a significant indicator of active cellular immunity. It increases in biological fluids in the course of infectious disease characterized by micro-organisms infecting the macrophages [29]. ADA has been proposed to be a useful surrogate marker for TB because it can be detected in body fluids such as pleural, pericardial and peritoneal fluid. The levels of ADA increase in TB because of the stimulation of T cells by mycobacterial antigens [30].

Adenosine deaminase (ADA) has been developed and widely used for the diagnosis of TB due to its simplicity, low cost, and quickly available results. Many studies have confirmed the high sensitivity and specificity of ADA (sensitivity 92% and specificity 89%) for early diagnosis of EPTB, such as tuberculous pleuritis, pericarditis, ascites and meningitis [32,33].

The main reason for the increased ADA levels in pleural effusion is the movement of T lymphocytes toward this area. When TB infection is controlled, growth-markers of lymphocytes decrease; leucocytes will decrease in serum ADA levels concurrent with the decrease in lymphocytes. Because of this, serum ADA level could be utilized as a treatment response index [29,30].

ADA assays can be performed in many health care centers with limited diagnostic facilities other than mycobacterial culture, PCR etc. In addition, it is cheap and it has good sensitivity. ADA may be used for early diagnosis of TB, especially in case of negative AFB smear from the body specimens. However, culture is still the gold standard and mandatory for the confirmatory diagnosis [33]. Many studies had reported about the correlation of ADA value in pulmonary TB with the healthy population, where the found significant positive correlation in ADA value in pulmonary TB patient [34,35]. In another study by Gupta *et al.*, 's find sensitivity, specificity, positive predictive value, and negative predictive value were 92.8%, 90%, 92.8%, and 90%, respectively, for diagnosis of TB in pleural effusion with an ADA level of more than 40 [36].

However elevated level of ADA have been reported in peritoneal, meningeal, pleural pericardial effusions in several non-tubercular diseases like hepatic cirrhosis, typhoid fever, infectious mononucleosis, brucellosis and bronchogenic carcinoma involving simulation of cell mediated immunity. So it's the job of health care worker to clinically correlate and corroborate the result with the other diagnostic finding.

## miRNA

miRNAs are small non coding RNAs molecules regulating multiple biological processes by interfering with mRNA translation” [37]. miRNAs are the largest gene defined as single-stranded RNAs ~22 nt in length (ranging 19–25 nt) generated from endogenous transcripts that can form local hairpin structures in silico. Discovery of miRNA resulted into several theories related to the process involved in its regulation and expression. O’Connell et al., describe three stages related to the function of miRNAs namely “(i) transcription, (ii) processing and (iii) subcellular localisation” [38]. Currently there are approximately 1,000 human miRNAs sequences were found in mammals and it targets about 60% of all genes. It plays a pivotal role in various biological processes including cell proliferation, cell cycle, cell growth, tissue organization, apoptosis and different metabolisms. In infectious diseases biology miRNAs play an extensive role in the maintenance of the regulatory signaling at the cellular level, which either provides protection from the disease or favors its persistency by inducing protected or unprotected signaling pathways, respectively [39]. In diseases condition miRNAs are found in serum, which were derived from the infected epithelial cells and other types of immune cells. The changes of several miRNA levels in plasma, serum, urine and saliva have been associated with various diseases [40]. Circulating miRNAs are stable which are protected from endogenous RNase activity. Several recent studies have established a significant correlation between the miRNA and the cause of diseases [41], therefore, today several miRNAs are being consider as molecular biomarkers for the diagnosis of human infectious diseases such as in tuberculosis, HIV/AIDS, Hepatitis, *H.pylori* infection [42].

Till date, several miRNAs have been reported as a molecular biomarker in infectious diseases, such as miRNA-150 and miRNA-146b-5p in human immunodeficiency virus (HIV); miRNA-122, miRNA-21, and miRNA-34a in hepatitis; miRNA-361-5p and miRNA-29c in tuberculosis; miRNA-16 and miRNA-451 in malaria and miRNA-181 in *Helicobacter pylori* infection [43,44].

## CXCL10/IP-10

C-X-C motif chemokine 10 (CXCL10) also known as interferon  $\gamma$ -induced protein 10 kDa (IP-10) or small-inducible cytokine B10 is a cytokine belonging to the CXC chemokine family. CXCL10 binds CXCR3 receptor to induce chemotaxis, apoptosis, cell growth and angiostasis. Modifications in CXCL10 expression levels have been associated with inflammatory diseases including infectious diseases, immune dysfunction and tumor development. CXCL10 is also recognized as a biomarker that predicts severity of various diseases. However, the mechanism of CXCL10 in the pathogenesis of infectious disease remains unclear.

CXCL10 have been shown to play a role in *Helicobacter pylori* and *Mycoplasma* [45,46]. Elevation of CXCL10 levels appears to be an early host response to scrub typhus infection [47] and is associated with severity of Legionnaire’s disease and tuberculosis (TB) [48]. Antimicrobial treatment significant decreased the level of CXCL10 in a murine model of *Mycoplasma pneumonia* [46]. Fewer studies on role of CXCL10 in fungal infections have been reported. Fungal infections abrogate CXCL10 expression in human cells. Impaired CXCL10 production contributes to the pathogenesis of cutaneous candidiasis caused by *Candida albicans* [49]. CXCL10 has been shown to be a novel biomarker for severity of Human African trypanosomiasis (HAT) caused by infection with sub-species of *Trypanosoma brucei*, *Plasmodium falciparum* and *Plasmodium vivax* malaria, *Toxoplasma gondii* and *Leishmania major* [50].

## Conclusion

In spite of the emergence of novel biomarkers, biomarker combinations and biomarker detection strategies of critical diseases such as sepsis, meningitis,



tuberculosis has been difficult and almost nonexistent. There is continued to be many knowledge gaps. Most of the novel biomarkers with strong performance values identified in this review were only evaluated in a small number of patients, indicating that there is a need for standardizing biomarker study methods and reporting performance results. The study gaps need to be delineated for the betterment of the test by collaboratively, by industry, academia, international health organizations and other institutions with the aligned goal of 1.) identifying promising host biomarkers that can distinguish latent tuberculosis and active tuberculosis and also should be able to differentiate between viral, fungal, bacterial & parasitic infection. 2) Developing these promising biomarkers into affordable rapid POC tests with practical implementation and utility in limited setting.

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