

The newest and classic biomarkers of sepsis in HIV-infected adult patients

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Abstract

Sepsis is one of the major causes of mortality of patients worldwide, and patients with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) are at higher risk of developing it. Given the importance of quick diagnosis, the demand for sepsis biomarkers is high. In this article, the authors reviewed the available sepsis biomarkers, and assessed whether the biomarkers were analyzed in patients with HIV/AIDS.

We investigated the available literature on classic inflammatory biomarkers, such as procalcitonin (PCT) and interleukin-6 (IL-6) as well as new biomarkers of sepsis, including soluble form of urokinase-type plasminogen activator receptor (suPAR), proadrenomedullin (proADM), soluble triggering receptor expressed on myeloid cells 1 (sTREM-1), growth arrest-specific 6 (Gas6), and microRNA (miRNA) in immunocompetent patients and patients living with HIV/AIDS. Various biomarkers have a diagnostic value (PCT, sTREM-1), others present a prognostic value (suPAR, Gas6, PSP, HBP), and some biomarkers have both values (IL-6, proADM, sCD14-ST, miRNA). Combining at least two different biomarkers has the best potential to bring high sensitivity and specificity of diagnosis.

To our knowledge, many of discussed novel inflammatory biomarkers, such as presepsin, pancreatic stone protein/regenerating protein (PSP/reg), or heparin-binding protein (HBP), were not yet studied in a population of patients with HIV/AIDS and sepsis.

So far, there is not a one biomarker used as a golden standard in diagnosis of sepsis. Monitoring at least two biomarkers might increase the chance of early detection of sepsis. Further research is needed to find biomarkers diagnosing sepsis in patients with AIDS.

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Introduction

According to the Third International Consensus Definition for Sepsis and Septic Shock from 2016, sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Dysregulation of immune response is caused by alterations in systemic cytokine levels. In immunocompetent patients, hyper-inflammatory response is then followed by lymphocyte impairment, and

thus leading to immunosuppression. The response in immunocompromised patients seems to be slightly different [2]. Weak and slow response of innate immune system in human immunodeficiency virus (HIV)-infected patients predisposes them to sepsis. Sepsis is one of the major causes of mortality of patients with HIV/acquired immunodeficiency syndrome (AIDS), with an incidence of about 1,000 per 100,000 population [3]. Symptoms of sepsis in immunosuppressed patients can be non-specific, and in patients with

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CD4+ cell count < 200 cells/μl, opportunistic infections (i.e., pulmonary tuberculosis, *Pneumocystis jiroveci* pneumonia, tuberculous, and cryptococcal meningitis) occur more frequently, making the diagnosis and management of patients with AIDS and sepsis more challenging than of immunocompetent patients.

Biomarkers, as defined in 2001 by the National Institute of Health are “characteristics that can be objectively measured and evaluated as indicators of normal biological processes, pathological processes, or pharmacological responses to a therapeutic intervention” are helpful in everyday clinical practice to diagnose and evaluate effectiveness of treatment [4]. Currently, the most commonly used classical biomarkers of infection are procalcitonin (PCT) and interleukin-6 (IL-6). There are numerous new markers of sepsis that are being investigated, such as soluble form of urokinase-type plasminogen activator receptor (suPAR), proadrenomedullin (proADM), soluble triggering receptor expressed on myeloid cells 1 (sTREM-1), growth arrest-specific protein 6 (Gas6), microRNA (miRNA), presepsin, heparin-binding protein (HBP), and pancreatic stone protein/regenerating protein (PSP/reg). By 2010, at least 178 different biomarkers of sepsis were reported in the literature [5].

In this article, the authors reviewed the available sepsis biomarkers and evaluated whether the biomarkers were analyzed in a group of patients with HIV/AIDS.

Biomarkers of sepsis

Commonly used classic inflammatory biomarkers are procalcitonin (PCT) and interleukin (IL)-6.

New inflammatory biomarkers include:

- suPAR – soluble form of urokinase-type plasminogen activator receptor,
- proADM – proadrenomedullin,
- sTREM-1 – soluble triggering receptor expressed on myeloid cells-1,
- Gas6 – growth arrest-specific protein 6,
- miRNA – microRNA,
- presepsin,
- PSP – pancreatic stone protein/regenerating protein (PSP/reg),
- HBP – heparin binding protein.

Classic inflammatory biomarkers

Procalcitonin

PCT is a peptide precursor of calcitonin produced by thyroid C cells. During bacterial or fungal infection, PCT is also detected in leukocytes, macrophages, and monocytes of intestines, lungs, and liver.

Bacterial toxins and tumor necrosis factor-alpha (TNF-α) are the strongest stimuli for PCT serum release. The level of PCT increases within 4 hours of initiation of the inflammatory process, and its' half-life is 22-26 hours.

It has been shown that low concentrations of PCT exclude the presence of bacteremia in patients with fever [6]. A meta-analysis reported sensitivity and specificity of PCT in bacteremia as 76% and 70%, respectively [7]. Some PCT scores show a correlation with certain pathogens isolated from blood, such as *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus*, or Gram-negative rods [8]. According to latest results, PCT is useful for individual assessment of the required duration of antibiotic therapy [9].

Several articles mention PCT as a marker, which increasing level would correlate with increased risk of hospital mortality of critically ill non-immunocompromised patients [10]. Such correlation was not present in a study by Bele *et al.*, who analyzed immunocompromised patients [11].

PCT is considered to be a more accurate biomarker of bacterial infection than C-reactive protein (CRP), but some authors state that PCT alone is not a good prognostic marker of sepsis, as similar levels appear in survivors and non-survivors of sepsis [8].

PCT and CRP might be useful markers in differentiating tuberculosis (TB) and community-acquired pneumonia (CAP). According to Kang *et al.*, PCT and CRP are higher in the course of the latter [12].

Procalcitonin in HIV/AIDS patients

During HIV infection, the PCT level is normal or slightly above upper normal limit. Similar observations were found in patients with HIV infection and *Pneumocystis jiroveci* pneumonia (PJP) or *Toxoplasma gondii* infection.

Schleicher *et al.* analyzed changes in PCT serum concentrations in HIV-infected patients with TB in comparison to HIV-infected patients with pneumococcal pneumonia. Patients with HIV and pneumococcal pneumonia presented with significantly higher levels of PCT and CRP than those with HIV and MTB infection [13].

Similar results were presented by Nyamande *et al.*, who found statistically significant differences in PCT concentrations between HIV-infected patients with bacterial pneumonia, TB, and PJP. The authors suggested using PCT as a marker for differentiating PJP from TB and other bacterial pneumonia in critically ill immunocompromised patients [14].

Patients with tuberculosis were also analyzed by Janssen *et al.*, who in a prospective cohort study with 60 HIV-positive patients with tuberculosis found a correlation between higher levels of procalcitonin and mortality [15].

Cytokines

In sepsis, both pro- and anti-inflammatory cytokines are released. Interactions between different cytokines in a cytokine storm are complex. Many cytokines involved in immune response to infection have been identified as biomarkers of inflammation and potential markers of sepsis. Those biomarkers can be a valuable addition to diagnostics as follow:

Pro-inflammatory cytokines: IL-1, IL-6, TNF-α, and tumor necrosis factor-beta (TNF-β) [16, 17].

IL-1 β , TNF- α , and IL-6 are good predictors of 28-day mortality in patients with sepsis. IL-6 is produced by MAP kinase and NF- κ B and other pathways in the signaling cascade of sepsis. Its levels rise before CRP and IL-6 itself, and is considered a marker of sepsis. A 10-fold more or higher than baseline value is considered a fairly early indication of sepsis [8].

Anti-inflammatory cytokines: IL-10, IL-4, transforming growth factor- β (TGF- β), and IL-13.

A recent mini review by Morrow *et al.* described interactions between IL-17, IL-27, and IL-33, and showed how these cytokines play their parts in immunological dysfunction during sepsis, revealing their potential as therapeutic targets. IL-27 produced by dendritic cells (DCs), monocytes, and macrophages, is a potent immunosuppressant. In 2012, Wong *et al.* demonstrated in their study that a concentration of IL-27 > 5 ng/ml had a good predictive value for diagnosis of critically ill children with a bacterial infection [18]. In another study conducted by the same authors in adults, the biomarker was not as useful as in the children cohort [19].

Cytokines in HIV/AIDS patients

In HIV-infected patients, IL-6 levels and age are independent risk factors of hospital mortality, irrespective of HIV/AIDS stage of disease. Prognosis of HIV-positive patients with sepsis could be assessed with a concentration level of several cytokines, including IL-6, IL-10, and granulocyte colony-stimulating factor (G-CSF) [20]. For proper evaluation of an outcome of sepsis, the balance between pro- and anti-inflammatory cytokines i.e., IL-6 : IL-10 ratio is useful, and this ratio could be also helpful for early prognosis of mortality among patients with PJP [21, 22].

New inflammatory biomarkers

Predicting the development of sepsis in HIV-positive patients is difficult. New biomarkers of inflammation are promising options for early diagnosis of sepsis. Biomarkers of inflammation presented below include those, which in several studies showed a correlation with sepsis and other inflammatory diseases. Some of these biomarkers were analyzed among HIV-infected patients, while others need further investigation.

Soluble form of urokinase-type plasminogen activator receptor (suPAR)

The urokinase-type plasminogen activator is present on monocytes, macrophages and other cells. During inflammation, it detaches from the cell surface and becomes a soluble form called 'suPAR'. Levels of suPAR are not specific for sepsis; this biomarker is more useful for prognosis of illness rather than for diagnosis of disease [19, 23]. In a meta-analysis carried out by Ni Wentao *et al.*, sensitivity and specificity for predicting mortality in patients with sepsis were 70% and 72%, respectively [24]. In a study by Suberviola *et al.*,

on the day of admission to ICU, acute physiology and chronic health evaluation II (APACHE II) and SOFA (sepsis-related organ failure assessment) scores were compared to CRP, PCT, suPAR, and proadrenomedullin (proADM) levels. In presented results, suPAR and proADM levels were better tools than CRP or PCT in prognosing sepsis and in-hospital mortality [25]. Henriquez-Camacho *et al.* in their study from 2014 observed that diagnostic value of this marker was not superior to other biomarkers, including CRP, PCT, or soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) [26]. However, as demonstrated in a study by Eugen-Olsen *et al.*, suPAR can be used as a predictive marker of mortality in patients with tuberculosis. Other studies showed that suPAR levels correlated with mortality in patients with *Streptococcus pneumoniae* and *Staphylococcus aureus* bacteremia [23].

SuPAR in HIV/IDS patients

Ever more attention is drawn to the topic of bacterial translocation and immune activation in patients with HIV. SuPAR is considered to be one of the markers of immune activation; it has not been analyzed as a biomarker of sepsis in HIV patients, but as a predictive biomarker of mortality. One of the first reports demonstrating an association between plasminogen activator system and HIV progression was published in 2000. Sidenius *et al.* showed that suPAR serum concentration correlated with mortality in HIV-infected patients [27].

In a Kirkegaard-Klitbo study with HIV-infected well-treated patients, non-AIDS comorbidity and all-cause mortality (cancer, cardiovascular, kidney, lung, and liver diseases) demonstrated an independent association with elevation of serum suPAR level [28]. It was shown that suPAR appeared to be an independent predictive marker of myocardial infarction in HIV-1-infected patients [29].

Proadrenomedullin (proADM)

ProADM present vasodilating and bactericidal activity. A combination of sequential organ failure assessment (SOFA) score and serum mid-regional proadrenomedullin (MR-proADM) can be used as predictors of 4-weeks mortality, with sensitivity and specificity of 66.7% and 86.8%, respectively [30]. In earlier works, proADM was considered a biomarker of prognostic value [25]. In a study from 2017, it was shown that proADM together with SOFA score can be used also as part of diagnosis. Spoto *et al.* analyzed serum PCT and MR-proADM serum concentration, and SOFA and quick SOFA (qSOFA) scores among patients with sepsis or septic shock. Mid-regional proadrenomedullin (MR-proADM) and SOFA presented similar to PCT-positive likelihood ratio in sepsis and septic shock, and those biomarkers can be included in diagnosis and prognosis of sepsis [31]. In another study, a combination of MR-proADM and PCT demonstrated a probability of 0.998 of diagnosing sepsis [32]. This is

yet another example on how using several markers instead of one presents higher probability of diagnosis of sepsis.

ProADM in HIV/AIDS patients

Proadrenomedullin, together with other markers (PCT and copeptin) and nasopharyngeal colonization density, were analyzed in 280 patients with HIV and community-acquired pneumonia. Proadrenomedullin, PCT, and copeptin were positively correlated with nasopharyngeal colonization density, with consecutive *p*-values of < 0.0001, 0.008, and 0.01. Quantitative nasopharyngeal density with > 8,000 copies/ml was an additional criterion for pneumococcal pneumonia [33]. Therefore, one might consider these markers in diagnosis of CAP in HIV-positive patients.

Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1)

Triggering receptor expressed on myeloid cells-1 (TREM-1) is a cell surface receptor, which number increases in response to severe fungal or bacterial infections. TREM-1 is mainly expressed on dendritic cells, monocytes, neutrophils, or macrophages. Its' soluble variant, soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), is released to urine, cerebrospinal fluid (CSF), or plasma during infection [34]. STREM-1 is also a promising inflammatory biomarker of pneumonia or sepsis-associated acute kidney injury (AKI) [35, 36]. In 11 studies, with a total of 1,795 patients, sTREM-1 sensitivity and specificity were evaluated as 79% and 80%, respectively [37]. STREM-1 and PCT, together with APACHE II and SOFA scores, can be useful methods of diagnosing sepsis [38]. Dolin *et al.* suggested combining three biomarkers, including sTREM-1, IL-6, and PCT in diagnosis of early-phase sepsis [8].

STREM-1 in HIV/AIDS patients

A recent publication on the importance of sTREM-1 assessed the ability of inflammatory response of macrophages or Kupffer cells (KC) to HIV or HCV stimulation. Results of this study show that HIV- and HCV-infected patients show higher TREM-1 expression and CD68 receptors positive cells. In addition, TREM-1 induction by HIV causes chronic inflammation in the liver, which may be important in HIV-infected patients' care [39]. We did not find any data about sTREM-1 as a biomarker in patients with HIV and sepsis.

Growth arrest-specific 6 (Gas6)

Gas6 belongs to plasma vitamin K-dependent proteins. Apart from being elevated in inflammation, Gas6 plasma levels have been shown to correlate with organ dysfunction and disease severity [40, 41]. A recent study by Stalder *et al.*, contrary to previous papers by other authors, demonstrated that plasma level of Gas6 measured at a 24-hour ICU admission, might predict in-hospital mortality in patients with sepsis [42].

Gas6 in HIV/AIDS patients

There is little clinical data on the significance of Gas6 in HIV-infected patients. It is known that HIV-1 infection induces apoptosis of HIV-1-infected cells, and other viruses are subjected to macrophage efferocytosis, which protects the host from mostly viral infections. In a study by Cua *et al.*, it has been confirmed that Gas6 protein and protein S, can mediate phagocytosis of HIV-1-infected cells, and that efferocytosis not only removes dead cells, but can also contribute to removal of macrophages of infected live cells [43].

MicroRNA (miRNA)

MicroRNAs are short sequences (20-24 nucleotides) of RNA that regulate gene expression. Even though miRNA represents only 1% of human genome, it regulates up to 60-90% of all protein-coding genes, and is essential for physiological and pathophysiological processes. MiRNAs regulate sepsis by targeting TNF and TLR/NF- κ B signaling pathways. Levels of miR-25 had a higher diagnostic accuracy for sepsis than CRP and PCT, and miR-25 could also be used for prognosis of sepsis. Serum levels of various miRNAs can be helpful in pathogen identification, including infections with *Staphylococcus aureus*, *Escherichia coli*, *Listeria monocytogenes*, *Mycobacterium tuberculosis*, *Salmonella enterica*, *Pseudomonas aeruginosa*, *Leishmania*, etc. [44]. Zhang *et al.* showed that miR-223-3p levels correlated with pneumocystis, and thus could be used as a biomarker of diagnostic value [45].

MiRNA in HIV/AIDS patients

Cellular miRNAs play an important role in the viral life cycle. The influence of miRNA on HIV replication needs further research, but it is considered to be a promising novel anti-HIV therapeutic [46]. MiRNA-155 is thought to be a biomarker of T cell activation and immune response after HIV infection [47].

Presepsin (sCD14-ST)

Presepsin is a 64-amino acids N-terminal fragment subtype of CD14 (sCD14-ST). Since 2004, presepsin is evaluated as a new biomarker of sepsis, with specificity and sensitivity of 83% and 78%, respectively [48, 49]. In a large review by Henriquez-Camacho *et al.* who analyzed inflammatory biomarkers used for diagnosing sepsis, presepsin showed to be one of the main and most accurate biomarkers. In the present review, according to many analysis and meta-analysis, presepsin proved to diagnose sepsis better than PCT [26]. In another study by Tong *et al.*, presepsin again proved to play an important role and predicting value of sepsis in comparison to PCT, CRP, or white blood cells (WBC). It only takes 17 minutes to test presepsin, and fast results make it a very good candidate for a sepsis biomarker [50]. In HIV/AIDS patients, presepsin has been mainly evaluated as one of the biomarkers of bacterial translocation. Although

Table 1. Biomarkers of sepsis analyzed in immunocompetent patients and/or patients with HIV/AIDS. Diagnostic or prognostic value of biomarkers of sepsis

Sepsis biomarker	Analyzed in immunocompetent patients	Analyzed in patients with HIV/AIDS	Diagnostic value	Prognostic value
PCT	Yes	Yes	Yes	Yes in immunocompetent patients
IL-6	Yes	Yes	Yes	Yes
suPAR	Yes	Not as a sepsis biomarker	No	Yes
proADM	Yes	Not as a sepsis biomarker	Yes	Yes
sTREM-1	Yes	Not as a sepsis biomarker	Yes	No
Gas6	Yes	Not as a sepsis biomarker	No	Yes
sCD14-ST	Yes	Not as a sepsis biomarker	Yes	Yes
PSP	Yes	No	No	Yes
HBP	Yes	No	No	Yes
miRNA	Yes	Not as a sepsis biomarker	Yes	Yes

analyzed carefully in many studies and considered by many authors a promising biomarker of sepsis, it has not been yet analyzed in patients with HIV/AIDS in that context.

Pancreatic stone protein/ regenerating protein (PSP/reg)

PSP/reg is secreted by pancreatic acinar cells into pancreatic juice and by subsets of intestinal and gastric cells. PSP/reg is considered to be a new protein present in acute phase of inflammation. Some studies showed that when measured within 24 hours of ICU admission, it may predict in-hospital mortality in patients with sepsis. In another study, PSP/reg, PCT, and high sensitivity-CRP (hs-CRP) were independent risk factors for prognosis of sepsis in pediatric patients. This analysis was not conducted on a cohort of adult patients, nor on a cohort of patients with HIV/AIDS [51].

Heparin-binding protein (HBP)

HBP is secreted from activated neutrophils after a contact with endothelium and from azurophil granules after internalization of bacteria by monocytes. In 2015, Linder *et al.* suggested that HBP could be used as a predictor of organ dysfunction during infection in patients admitted to emergency departments [52].

In the next years, in many trials, significance of HBP as a biomarker of sepsis and inflammation confirmed effectiveness of HBP [53, 54]. However, we did not find any papers analyzing HBP as a sepsis biomarker in HIV-infected patients.

Discussion

HIV infection leads to disorders of the humoral and cellular immune response. Initially, the number of CD4+ T lymphocytes is reduced, but with time it grows, only to be fol-

lowed by a decrease in numbers again. In subsequent years, the function of CD4+ T lymphocytes is irreversibly damaged, leading to changes in the production of various cytokines. These changes in the immune response have led to a hypothesis that HIV might lead to further changes in the host response in sepsis. But in the era of treating all patients with HIV, independent of CD4+ cell count, changes in the immune system in patients on antiretroviral treatment (ART) do not differ much from that in immunocompetent individuals. Therefore, the focus should be on prompt diagnosis and treatment of patients with AIDS who are not yet on ART.

About 12-31% of admissions of patients with HIV to ICU is due to sepsis [55]. In a retrospective study by Vidal-Cortes *et al.*, a total of 104 HIV-infected patients were admitted to ICU, in which the most frequent sites of infection were the lungs (more than 65.0%), followed by central nervous system (16.4%), urinary tract infection, and infective endocarditis, both occurring in 4.9% of patients. ICU hospital mortality rate was 41.9%. The most common pathogens included *Streptococcus pneumoniae* (28.8%), *Pneumocystis jirovecii* (13.6%), *Toxoplasma gondii* (8.5%), *Escherichia coli*, and *Haemophilus influenzae* (both, 5.1%) [56].

In previous studies, patients with HIV/AIDS and sepsis had a higher mortality than those with sepsis but without HIV [57, 58]. In 2013, Silva *et al.* in a prospective study showed that although the severity of sepsis and prognostic scores were similar between patients with and without HIV, the mortality was higher for HIV patients. Mycobacterial and fungal etiologies were the most frequent causes of infections, leading to pulmonary and abdominal diseases [55]. A different result was presented by Wiewel *et al.* in 2016, who in a prospective study of 1,889 patients with sepsis (32 patients with HIV), measured 14 biomarkers (INF- α , IL-1 β , IFN- γ , IL-6, IL-8, IL-10, IL-13, ICAM, soluble E-selectin, angiopoetin-1 and 2, protein C, and antithrombin), which play an important role in sepsis, and showed that the concentration level of these biomarkers were similar in patients

with and without HIV. Moreover, the disease severity and outcome was similar for patients with and without HIV. The only statistically significant difference was that patients with HIV had a higher prevalence of pneumonia [59].

Differences in results might be that patients' selection and setting of the study differed. In a paper by Wiewel *et al.*, 70.7% ($n = 29$) of patients were already on treatment, and 47.4% ($n = 18$) had an undetectable viral load [59]. Patients with an advanced HIV disease (CD4+ cell count < 200 cells/ μ l or AIDS-defining illness) are at higher risk of developing opportunistic infections (OIs), and with unknown HIV status, the detection and treatment might be delayed.

Even though in the era of ART, main causes of death of HIV-positive patients are non-AIDS-related events, and about 49% of newly diagnosed HIV cases in Europe are late presenters (CD4+ cell count < 350 or with an AIDS-related event, regardless of CD4+ cell count) [60]. Therefore, these cases constitute a group of patients that need prompt diagnosis and treatment.

Early diagnosis of OIs could prevent the development of sepsis. Markers that might be useful in differentiating community-acquired pneumonia (CAP) from tuberculosis are C-reactive protein (CRP), procalcitonin (PCT), and soluble form of urokinase-type plasminogen activator receptor (suPAR).

Even though CRP is not a sepsis biomarker itself, it is an important marker of inflammation, and in HIV/AIDS patients, it might be important for diagnosis of TB and CAP. In a meta-analysis evaluating diagnostic accuracy of CRP (10 mg/l cut-off point) among patients with *Mycobacterium tuberculosis* (MTB), it was shown that CRP could be used to screen for tuberculosis (TB) in patients with HIV/AIDS [61]. Similar results were also showed by Bedell *et al.*, where elevated CRP was associated with confirmed or probable TB infection in a group of 452 HIV-infected adults from Malawi [62].

To our knowledge, many of the biomarkers of sepsis discussed in this article have not yet been analyzed in patients with HIV/AIDS. The value of the biomarkers discussed in this paper is summarized in Table 1. Combining at least two different biomarkers has the best potential to bring high sensitivity and specificity of diagnosis of sepsis.

Conclusions

So far, there is not a one biomarker used as a golden standard in the diagnosis of sepsis. Using two or more biomarkers might increase the chance of early detection of sepsis, and thus be beneficial for patients. To our knowledge, many biomarkers were not yet analyzed in a population of patients with AIDS. Further research is needed in finding biomarkers diagnosing sepsis in HIV/AIDS patients.

Conflict of interest

The authors declare no conflict of interest.

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