Biochemistry **Mini-Review**
International Journal of Clinical and Diagnostic Research **ISSN 2395-3403**
Volume 8, Issue 5 , Sep-Oct 2020

BIOCHEMICAL APPROACH TO SEPSIS: A MINIREVIEW

Priyanka A[1*], Venkatesha[2], Wilma Delphine Silvia CR[3], Venkata BharatKumar Pinnelli[4]

ABSTRACT

Sepsis remains a major reason behind morbidity and mortality among all age groups. The ability to promptly and accurately diagnose sepsis with supported clinical evaluation and laboratory blood tests remain challenging. Recent advances in molecular technologies have increased investigations into the utility as diagnostic tools for sepsis. A systems-level understanding of sepsis, obtained by using new technologies may cause new diagnostic tools for sepsis. Despite the emerging need, future studies need to address the challenges of integrating with laboratory and clinical data so as to translate outcomes into precision medicine for sepsis. More research is required to validate the recent findings so as to integrate clinical and laboratory findings for future translation into precision medicine for sepsis. This mini review will discuss the possible applications and identification of recent biomarkers and diagnostic signatures for sepsis.

Authors Affiliations:

[1,2,3] Department of Biochemistry, Bowring and Lady Curzon Medical College and Research Institute, Bangalore-560001

[4] Department of Biochemistry, Vydehi Institute of Medical Sciences and Research Centre, Bangalore-560066

Keywords: Sepsis, Inflammatory, Infection, Biomarkers

***Corresponding Author:**

Ms. Priyanka A

Tutor, Department of Biochemistry

Bowring and Lady Curzon Medical College and Research Institute

Shivajinagar, Bangalore – 560001

Contact No: 8151085890

annapoornapriya102@gmail.com, bowringbiochem@gmail.com

INTRODUCTION

Sepsis is synonymously referred to as septicemia or systemic inflammatory response syndrome (SARS). Sepsis is characterized by a deregulated response to microbial infection and life-threatening organ dysfunction regularly complication in hospitalized patients[1]. Sepsis may possibly be a systemic inflammatory response syndrome that contains a proven or suspected microbial etiology [2]. Sepsis occurs when chemicals released within the bloodstream to fight an infection triggered inflammation throughout the body. This might cause a cascade of changes that damage multiple organ systems, leading them to fail, severity sometimes leading to death [3]. Symptoms include fever, dyspnea, hypotension, tachycardia disarray & muddiness. Sepsis is most ordinarily found in people who have chronic conditions, like diabetes, kidney or lung disease, or cancer, several co morbidities and who infected with SARS, Corona virus disease (COVID-19)& Influenza like infection(ILI)[4]. Early diagnosis of sepsis is required critically to avoid unnecessary usage of antimicrobial agents and for proper antibiotic treatment through the screening by using biomarkers [5]. Sepsis biomarkers can have important diagnostic, therapeutic, and prognostic functions. A recent review detailed nearly 180 biomarkers that are evaluated including IL-6, IL-8, lactate, C-Reactive Protein (C-RP) soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), and procalcitonin (PCT) and Scd14-subtypes (persepsin) [6].The studies of those biomarkers on sepsis concerning the diagnosis, assessment, antibiotic treatment and prognosis have attracted extensive attention from researchers[7] . This mini review presents the gist of sepsis biomarkers being used at present and may be used in the future.

SEPSIS BIOMARKERS

Sepsis is defined as systemic inflammatory response syndrome (SIRS) caused by infection [8-10].However, infections is difficult to substantiate. Fever, tachycardia, hypotension, and other sign abnormalities founding SIRS don't seem to be specific for infection and overlap with noninfectious etiologies presenting with systemic inflammation. There is not any gold standard for diagnosing infection, and though blood cultures processed with standard microbiologic techniques are a frequent diagnostic step, their likelihood of returning with the pathogen of interest depends on a variety of things, including prior antibiotic therapy [11,12]. There are many attempts to strengthen clinical higher cognitive operation with diagnostic tests to increase sensitivity and specificity when diagnosing and treating sepsis

and bacteremia. Initial studies employed fever and leukocytosis to define sepsis [13], though these tests were nonspecific. Subsequent studies focused on erythrocyte rate (ESR) and C-reactive protein (CRP) to help within the diagnostic algorithm but suffered from the identical lack of specificity. PCT has been the foremost studied and felt to hold the foremost promise. Sepsis biomarkers may provide information beyond what's available using other metrics and can therefore help to tell clinical decision-making and potentially improve patient management. Many potential sepsis biomarkers are proposed, procalcitonin (PCT) and CRP (CRP) being the foremost frequently used.

THE PRESENT SEPSIS BIOMARKERS:

C- REACTIVE PROTEIN (CRP)

CRP is an acute-phase reactant that consists of five 23-kDa subunits and its hepatic synthesis starts rapidly after a stimulus with rise. Elevated CRP levels in sepsis are correlated with increased risk of death and organ failure [14], but partly thanks to the persistence of elevated levels, were unable to predict survival when evaluating CRP trends [15, 16]. CRP has been used successfully during initial sepsis diagnosis, but its specificity is further reduced later within the course thanks to persistently elevated levels [17]. CRP has been found to be significantly elevated in sepsis thanks to gram negative infections compared with gram positive infections suggesting a special immune modulatory response [18]. Even PCT changes occur a little late but CRP and LDH are the first to rise. Clinically these three are dangerous.

PROCALCITONIN (PCT)

Procalcitonin could be a 116 amino alkanoic acid polypeptide precursor for the hormone calcitonin. Procalcitonin offers favorable kinetics for a biomarker: rising before two hours [19], reliably detectable between 2 and 4 hours, peaking at 6 hours, and maintaining a plateau through 8 and 24 hours [20] PCT is released from many cell types distributed throughout the body [21] and is induced by interleukin-1β, tissue necrosis factor (TNF)-α, IL-6, and lipopoly saccharides and can be attenuated by interferon-γ that is elevated during viral infections [22]. These and other observations have led to the extensive evaluation of PCT as a marker of sepsis and blood stream infection. There are several meta-analyses evaluating PCT as a diagnostic marker in sepsis [23, 24–26]. While the sooner meta-analyses had conflicting results and were limited by populations studied and sepsis definitions. PCT best predicted septicemia compared with IL-6 and CRP with 73%

sensitivity and 70% specificity for bacteremia with acute off of 0.5ng/mL. Thanks to its ability to assist differentiate between viral and bacterial infections, PCT has been evaluated for its ability to guide decisions for appropriate antibiotic therapy.[27]

PERSEPSIN

Presepsin is another name for the sCD14 subtype (sCD14-ST), may be a greenhorn biomarker related to sepsis. Soluble CD14 subtype is one fragment of CD14 soluble that's a molecular fragment produced by plasma protease activity during the inflammatory process [28]. Presepsin is present within the cell membranes of macrophages, monocytes and granulocyte cells and said to play a task for the intracellular transduction of endotoxin signals [29]. Presepsin has close relation with infection and is found to extend significantly in sepsis. compared to PCT, presepsin showed similar diagnostic accuracy for sepsis with sensitivity 0.78 However, there are some superiority of presepsin over PCT. Presepsin raised earlier within the event of infection therefore are visiting be utilized in earlier and faster in sepsis.

THE FUTURE SEPSIS BIOMARKERS:

TRIGGERING RECEPTOR EXPRESSED ON MYELOID CELLS-1 (TREM-1)

Triggering receptor expressed on myeloid cells (TREM) 1 could be a cell surface molecule implicated within the propagation of the inflammatory response. Engagement of TREM-1 induces the assembly of inflammatory chemokines and cytokines, like interleukin (IL) 8 and tumor necrosis factor (TNF) α. Triggering receptor expressed on myeloid cells-1 (TREM-1) was reported to be up regulated in various inflammatory diseases similarly as in sepsis; TREM-1 expression is expounded to elevations in soluble TREM-1 (sTREM-1). Expression of TREM-1 is elevated in vitro within the presence of bacteria or fungi still as peritoneal fluid and tissue from infected patients [30,31] but remains at normal levels in non-infectious inflammatory conditions and may be a therapeutic target for sepsis [32].

Some studies have shownsTREM-1to be superior to CRP and PCT [33] but other studies have shown that sTREM1 has poor discriminatory power compared with routinely available parameters [34]. A recent meta-analysis found that the sensitivity of sTREM-1 for the diagnosis of bacterial infection was 82% which the specificity was 86% [35]. While IL-6 and IL-8 levels are shown to be elevated

in sepsis and associated with severity and outcome[36],they have not been found to be superior to PCT as biomarkers [37, 38]. These cytokines are found to be elevated in neutropenic fever [39] and neonatal sepsis [40] but are less useful within the adult population [41]. Interleukin27 (IL-27) presented the highest predictive power. The identical group subsequently validated their findings by measuring serum levels of IL-27 in a very separate study and located serum IL-27 concentrations were significantly higher in patients with sepsis compared with non infected patients yielding 92% specificity and 91% PPV for bacterial infection in critically ill children.

PRO ADRENOMEDULLIN (ADM)

In recent years, the interest of the scientific community has focused on adrenomedullin (ADM), a peptide that's produced by heart, medulla, lungs, kidneys, and vascular endothelium during physiological stress. ADM was initially studied for its vasodilating properties. Lipopolysaccharides and pro-inflammatory cytokines, like TNF-α and IL-1β, rapidly promote ADM production through increased ADM natural phenomenon in several tissues [42]. The discharge of ADM into the bloodstream regulates the vascular tone, guaranteeing adequate organ perfusion; it also results in potent pore-mediated antibacterial activity and in immune modulation through the induction of apoptosis. At the short arm of human chromosome 11 (p11.1–3) ADM gene is found and it consists of three introns and four exons. The mRNA encodes the knowledge for the synthesis of a pre pro hormone of 185 aminoacids, called pre pro adrenomedullin, which is subsequently degraded into a 164-aminoacid-peptide, called pro adrenomedullin (ProADM), through cleavage of the signal peptide [43]. ProADM is utterly cleaved by an endogenous peptidase, peptidyl hydroxyglycine α-amidating lyase, into four different peptides: ADM, the amino terminal peptide of ProADM (PAMP), adrenotensin, and mid regional pro adreno medullin (MR-ProADM) [44]. ProADM and ADM are secreted in equimolar amounts during this post-translational modulation. However, ADM is rapidly metabolized and eliminated from the bloodstream, which makes its levels hardly measurable. ProADM displays higher stability in circulation and it's easily detectable. within the adult population, it has been documented that ADM and ProADM levels rapidly rise in sepsis and high bacterial infections, that they are related to the severity of the disease, which they accurately predict the possibility of organ failure and mortality. Despite that literature being rich of studies on ProADM within the

adult population, data on its performance within the paediatric setting are limited.

SOLUBLE UROKINASE- TYPE PLASMINOGEN ACTIVATOR RECEPTOR (SUPAR)

Recently, the soluble style of the urokinase-type proteolytic enzyme receptor (suPAR) has attracted scientific interest because it seems to discriminate better than other biomarkers among patients with different severities of illness [45]. The urokinase-type urokinase (uPA) system consists of a protease, a receptor (uPAR) and inhibitors. suPAR takes part in various immunological functions, including cell adhesion, migration, chemotaxis, proteolysis, immune activation, tissue remodeling, invasion and signal transduction [46]. As early as 1995, elevated plasma suPAR levels were reported in an exceedingly small group of septic medical care unit (ICU) patients [47]. During endotoxemia, suPAR expression is increased on peripheral blood mononuclear cells [48] as on monocytes and granulocytes [49]. However, although suPAR serum concentrations were increased after administration of high-dose endotoxin, low-dose endotoxin failed to significantly increase plasma suPAR levels in vivo [50]

MONOCYTE CHEMO-ATTRACTANT PROTEIN 1 (MCP-1)

To date, all of the cytokines investigated as prognostic biomarkers for sepsis have lacked sufficient specificity or sensitivity to be routinely employed in clinical practice. Severe trauma can induce exacerbation of systemic inflammation, which regularly progresses to sepsis resulting in a lethal outcome. MCP-1 plays a key pathogenic role within the pathogenesis mechanisms of leading sepsis.

ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION (APACHE)

One marker employed in the ICU is that the Acute Physiology and Chronic Health Evaluation (APACHE) II score, which has been shown to be associated with clinical outcomes in various critically ill patient cohorts. The mainstay within the proper management of sepsis is early recognition of the patient at high risk for death. This is often traditionally supported the appliance of severity scores and serum biomarkers. The foremost widely applied score is that of the Acute Physiology and Chronic Health Evaluation II (APACHE II).

NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN (NAGL)

Neutrophil gelatinase-associated lipocalin (NGAL) is released from kidney tubular cells under stress moreover as from neutrophils during inflammation. It's been suggested as a biomarker for acute kidney injury (AKI) in critically ill patients with sepsis to gauge clinical usefulness of urine NGAL (uNGAL). It increases rapidly in serum and urine not only in conjunction with renal tubular injury, but also in bacterial infections, non-infectious systemic inflammatory response syndrome, and chronic and systemic diseases without bacterial infection [51]

MACROPHAGE MIGRATION INHIBITORY FACTOR (MIF)

Macrophage migration inhibitory factor (MIF) may be a pleiotropic inflammatory mediator that's considered the primary cytokine activity to be reported [52-54]. MIF is structurally unique; its monomeric relative molecular mass is 12.5 kDa, with two anti-parallel alpha-helices and 6 beta pleated sheets forming an extended secondary structure of the molecule. Biophysical studies indicate that in its active form, MIF may be a homo trimeric molecule with topologic homology to only 1 other mammalian proteins, the enzyme D-dopachrome-tautomerase [55]. Plasma MIF concentrations is elevated to extremely high levels in several inflammatory disorders. The primary indications that MIF could be involved in systemic infection and in sepsis, and might function as biomarker. The present and future biomarkers for sepsis are shown in Table 1.

Table1: BIOMARKERS OF SEPSIS

The present Sepsis Biomarkers	Procalcitonin (PCT)
	C- Reactive Protein(C-RP)
	Persepsin
The future Sepsis Biomarkers	Triggering receptor expressed on myeloid cells-1 (TREM-1)
	Interleukin27 (IL-27)
	Pro Adrenomedullin (ADM)
	Soluble –Urokinase- type Plasminogen activator receptor (suPAR)
	Monocyte chemoattractant protein 1(MCP-1)
	Acute Physiology And Chronic Health Evaluation (APACHE)
	Neutrophil gelatinase-associated lipocalin (NAGL)
	Macrophage Migration Inhibitory Factor (MIF)

CONCLUSION:

In the last few years, the increased number of high-risk patients because the selection and propagation of multidrug-resistant organisms has raised new challenges within the management of sepsis. Advancing age increases the prevalence of frail patients with chronic conditions linked to increased risk of sepsis, which sometimes are often severe and difficult to diagnose. Beside many, extensive researches are done to spot biomarkers useful for diagnosis, definition of severity, management, and follow-up of sepsis. To date, although with some limitations, the foremost validated and clinically informative biomarker is PCT, preferably employed in combination with C-reactive protein. These molecules provide useful information for diagnosis and prognosis in several clinical conditions, including patients with mild disease (probable or possible sepsis) still as those with severe sepsis or septic shock. Many other biomarkers are being investigated and tested in clinical studies. In future many other molecular level investigations can be done using different biomarkers for the diagnosis and prognosis of sepsis. There is a critical need to find biomarkers for sepsis which has a high mortality to predict the outcome.

Conflict of Interest Statement:

There is no conflict of interest.

REFERENCES:

1. Venet, Fabienne, and Guillaume Monneret. "Advances in the understanding and treatment of sepsis-induced immune suppression." *Nature Reviews Nephrology* 14.2 (2018): 121.
2. Piantino, Jessica H., et al. "Culture negative sepsis and systemic inflammatory response syndrome in neonates." *NeoReviews* 14.6 (2013): e294-e305.
3. Tsiotou, Adelais G., et al. "Septic shock; current pathogenetic concepts from a clinical perspective." *Medical Science Monitor* 11.3 (2005)
4. Gotts JE, Matthay MA. Sepsis: pathophysiology and clinical management. *BMJ*. 2016. Published 2016 May 23
5. Vijayan, Ashitha L et al. “Procalcitonin: a promising diagnostic marker for sepsis and antibiotic therapy.” *Journal of intensive care* vol. 5 51. 3 Aug. 2017
6. Faix, James D. “Biomarkers of sepsis.” *Critical reviews in clinical laboratory sciences* vol. 50,1 (2013): 23-36.

7. Zou, Qi et al. "Presepsin as a novel sepsis biomarker." *World journal of emergency medicine* vol. 5,1 (2014):
8. R.P.Dellinger, M.M.Levy, and J.M.Carlet, "Surviving Sepsis Campaign: international guidelines for management of severe sepsisandsepticshock,"*CriticalCareMedicine*,vol.36,pp.296– 327,2008.
9. P. Khilnani, S. Deopujari, and J. Carcillo, "Recent advances in sepsis and septic shock, "*Indian Journal of Pediatrics*,vol.75,no. 8,pp.821–830,2008.
10. M. M. Levy, M. P. Fink, J. C. Marshall et al., International sepsis definitions conference, "*Critical Care Medicine*,vol.31,no.4,pp.1250–1256,2003.
11. D. Flayhart, A. P. Borek, T. Wakefield, J. Dick, and K. C. Carroll, "Comparison of BACTEC PLUS blood culture media to BacT/Alert FA blood culture media for detection of bacterial pathogens in samples containing therapeutic levels of antibiotics, "*Journal of Clinical Microbiology* ,vol.45,no.3,pp.816–821, 2007
12. R.Zadroga, D.N.Williams, R.Gottschalletal.,"Comparison of 2 blood culture media shows significant differences in bacterial recovery for patients on antimicrobial therapy," *Clinical Infectious Diseases* ,vol.56 ,no.6, pp.790–797, 2013.
13. C. Pierrakos and J. L. Vincent, "Sepsis biomarkers: a review," *CriticalCare*, vol.14, no.1, article R15,2010
14. S. M. A. Lobo, F. R. M. Lobo, D. Peres Bota et al., "C-reactive protein levels correlate with mortality and organ failure in critically III patients,"Chest,vol.123,no.6,pp.2043–2049,2003.
15. K. Tschaikowsky, M. Hedwig-Geissing, G. G. Braun, and M. Radespiel-Troeger, "Predictive value of procalcitonin, interleukin-6, and C-reactive protein for survival in postoperative patients with severe sepsis, "*Journal of Critical Care*, vol.26,no. 1,pp.54–64,2011.
16. K. Tschaikowsky, M. Hedwig-Geissing, J. Schmidt, and G. G. Braun, "Lipopoly saccharide-binding protein for monitoring of postoperative sepsis: complemental to C-reactive protein or redundant?",vol.6, no.8 ,2011.
17. Y.Sakr, U.Burgett, F.E.Nacul, K.Reinhart, and F.Brunkhorst, "Lipopolysaccharide binding protein in a surgical intensive care unit :amarkerof

sepsis?"*CriticalCareMedicine*,vol.36,no.7, pp.2014–2022,2008.

18. F. M. Brunkhorst, U. Heinz, and Z. F. Forycki, "Kinetics of procalcitonin in iatrogenic sepsis, "*Intensive Care Medicine*, vol. 24,no.8,pp.888–889,1998.
19. P.Dandona, D.Nix, M.F.Wilsonetal., "Procalcitonin increase after endotoxin injection in normal subjects,"*Journal of Clinical Endocrinology and Metabolism*, vol. 79, no. 6, pp. 1605–1608, 1994.
20. B.M¨uller, J.C.White, E.S.Nyl´en, R.H.Snider, and K.L.Becker, "Ubiquitous expression of the calcitonin I gene in multiple tissues in response to sepsis, "*Journal of Clinical Endocrinology andMetabolism*,vol.86,no.1,pp.396–404,2001.
21. P. Linscheid, D. Seboek, E. S. Nylen et al., "In vitro and in vivo calcitonin Ig ene expression in parenchymal cells :anovel product of human adipose tissue," *Endocrinology*, vol. 144, no. 12,pp.5578–5584,2003.
22. B.Uzzan, R.Cohen, P.Nicolas, M.Cucherat, and G.-Y.Perret, "Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: a systematic review and meta analysis," Critical Care Medicine, vol. 34, no. 7, pp. 1996–2003, 2006.
23. B.M.Tang, G.D.Eslick, J.C.Craig, andA.S.McLean, "Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis," *The Lancet Infectious Diseases*,vol.7,no.3,pp.210–217,2007.
24. L.Simon, F.Gauvin, D.K.Amre, P.Saint-Louis, and J.Lacroix, "Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis," *Clinical Infectious Diseases*,vol.39,no.2,pp.206–217,2004.
25. C. Wacker, A. Prkno, F. M. Brunkhorst, and P. Schlattmann, "Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis," *The Lancet Infectious Diseases*, vol. 13,no.5,pp.426–435,2013.
26. C. Pierrakos and J. L. Vincent, "Sepsis biomarkers: a review," CriticalCare, vol.14, no.1,2010.
27. Zou Q, Wen W, Zhang X. Presepsin as a novel sepsis biomarker. *World Journal of Emergency Medicine*. 2014;5(1):16-19

28. Agilli M, Sener I, Yesildal F, Honca T, Aydin I, Akgul EO, et al. A new marker for the diagnosıs of sepsis: Presepsin. *Journal of Investigational Biochemistry*. 2012;1(1):55-57
29. A. Bouchon, J. Dietrich, and M. Colonna, "Cutting edge: inflammatory responses can be triggered by TREM-1, a novel receptor expressed on neutrophils and monocytes," *Journal of Immunology*,vol.164, no.10, pp.4991–4995, 2000.
30. J.Cohen,"TREM-1insepsis,"The Lancet,vol.358, no.9284,pp. 776–778,2001.
31. A. Bouchon, F. Facchetti, M. A. Weigand, and M. Colonna, "TREM-1 amplifies inflammation and is a crucial mediator of septic shock, "Nature, vol.410, no.6832, pp.1103–1107, 2001.
32. S. Gibot, M. N. Kolopp-Sarda, M. C. Bene, A. Cravoisy, B. Levy, and G. C. Faure, "Plasma level of a triggering receptor expressed on myeloidcells-1:its diagnostic accuracy in patients with suspected sepsis,"*Annals of Internal Medicine*,vol.141,pp. 9–15,2004.
33. J. Latour-P´erez, A. Alcal´a-L´opez, M. A. Garc´ıa-Garc´ıa et al., "Diagnostic accuracy of sTREM-1 to identify infection in critically ill patients with systemic inflammatory response syndrome," *Clinical Biochemistry*, vol. 43, no. 9, pp. 720–724, 2010.
34. J.Jiyong, H.Tiancha, C.Wei, and S.Huahao, "Diagnostic value of the soluble triggering receptor expressed on myeloid cells-1 in bacterial infection :a meta-analysis, "*Intensive Care Medicine*, vol.35,no.4,pp.587–595,2009.
35. K. Hamano, H. Gohra, H. Noda et al., "Increased serum interleukin-8 :correlation with poor prognosis in patients with postoperative multiple organ failure ,"*World Journal of Surgery*, vol.22,no.10,pp.1077–1081,1998.
36. S. Harbarth, K. Holeckova, C. Froidevaux et al., "Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis, "*TheAmerican Journal of Respiratory and Critical Care Medicine*,vol.164,no.3, pp.396–402,2001.
37. E.L.Tsalik, L.B.Jaggers, S.W.Glickmanetal., "Discriminative value of inflammatory biomarkers for

suspected sepsis, ”*Journal of Emergency Medicine*, vol.43,no.1,pp.97–106,2012.

38. A. Engel, E. Mack, P. Kern, and W. V. Kern, “An analysis of interleukin-8, interleukin-6 and C-reactive protein serum concentrations to predict fever, gram-negative bacteremia and complicated infection in neutropenic cancer patients, ”Infection, vol.26,no.4,pp.213–221,1998.
39. R. Berner, C. M. Niemeyer, J. U. Leititis et al., “Plasma levels and gene expression of granulocyte colony-stimulating factor, tumor necrosis factorα, interleukin (IL)-1β, IL-6, IL-8, and soluble intercellular adhesion molecule-1in neonatal early onset sepsis,”*PediatricResearch*,vol.44,no.4,pp.469–477,1998.
40. C. S. Calfee, B. T. Thompson, P. E. Parsons, L. B. Ware, M. A. Matthay, and H. R. Wong, “Plasma interleukin-8 is not an effective risk stratification tool for adults with vasopressor dependent septic shock,” Critical *Care Medicine*, vol. 38, no. 6, pp.1436–1441,2010.
41. Zudaire, E.; Portal-Núñez, S.; Cuttitta, F. The central role of adreno medullin in host defense. J. Leukoc. Boil. 2006, 80, 237–244.
42. Valenzuela-Sánchez, F.; Valenzuela-Méndez, B.; Rodríguez-Gutiérrez, J.F.; Estella-García, Á.; González-García, M.Á. New role of biomarkers: Mid-regional pro-adrenomedullin, the biomarker of organ failure. *Ann. Transl. Med*. 2016, 4, 329.
43. Huttunen R, Syrjanen J, Vuento R, Hurme M, Huhtala H, Laine J, Pessi T, Aittoniemi J: Plasma level of soluble urokinase-type plasminogen activator receptor as a predictor of disease severity and case fatality in patients with bacteraemia: a prospective cohort study. *J Intern Med 2011*, 270:32-40.
44. Eugen-Olsen J: suPAR as a marker of disease severity and risk of mortality in sepsis. J Intern Med 2011, 270:29-31.
45. Mizukami IF, Faulkner NE, Gyetko MR, Sitrin RG, Todd RF: Enzyme-linked immunoabsorbent assay detection of a soluble form of urokinase plasminogen activator receptor in vivo. Blood 1995, 86:203-211.
46. Ostrowski SR, Plomgaard P, Fischer CP, Steensberg AS, Moller K, HoyerHansen G, Pedersen BK, Ullum H: Interleukin-6 infusion during human endotoxaemia inhibits in vitro release of the urokinase receptor from

peripheral blood mononuclear cells. *Scand J Immunol* 2005, 61:197-206.

47. Dekkers PE, ten Hove T, te Velde AA, van Deventer SJ, van der PT: Upregulation of monocyte urokinase plasminogen activator receptor during human endotoxemia. *Infect Immun 2000*, 68:2156-2160.
48. Juffermans NP, Dekkers PE, Verbon A, Speelman P, van Deventer SJ, van der PT: Concurrent upregulation of urokinase plasminogen activator receptor and CD11b during tuberculosis and experimental endotoxemia. *Infect Immun 2001*, 69:5182-5185.
49. Ostrowski SR, Plomgaard P, Fischer CP, Steensberg AS, Moller K, HoyerHansen G, Pedersen BK, Ullum H: Interleukin-6 infusion during human endotoxaemia inhibits in vitro release of the urokinase receptor from peripheral blood mononuclear cells. *Scand J Immunol 2005*, 61:197-206.
50. Schmidt-Ott KM, Mori K, Li JY, Kalandadze A, Cohen DJ, Devarajan P, et al. Dual action of neutrophil gelatinase-associated lipocalin. *J Am Soc Nephrol*. 2007;18(2):407–13.
51. Rich AR, Lewis MR. The nature of allergy in tuberculosis as revealed by tissue culture studies. Bull Johns Hopkins Hosp. 1932;50:115–31.
52. George M, Vaughn JH. In vitro cell migration as a model for delayed hypersensitivity. *Proc Soc Exp Biol Mes*. 1962; 111:514–21.
53. David JR. Delayed hypersensitivity in vitro: its mediation by cell-free substances formed by lymphoid cell-antigen interaction. *Proceedings of the National Academy of Sciences of the United States of America.* 1966;56(1):72–7.
54. Sun HW, Swope M, Cinquina C, Bedarkar S, Bernhagen J, Bucala R, et al. The subunit structure of human macrophage migration inhibitory factor: evidence for a trimer. *Protein Engineering*. 1996; 9(8):631–5.