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DIAGNOSTIC AND PROGNOSTIC SEPSIS BIOMARKERS IN CRITICAL CARE PATIENTS-A SYSTEMATIC REVIEW

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POOJA YADAV

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DIAGNOSTIC AND PROGNOSTIC SEPSIS BIOMARKERS IN CRITICAL CARE PATIENTS-A SYSTEMATIC REVIEW

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I hereby declare that this dissertation entitled **"** DIAGNOSTIC AND PROGNOSTIC SEPSIS BIOMARKERS IN CRITICAL CARE PATIENTS-A SYSTEMATIC REVIEW*"* is bonafide and genuine research work carried out by me under the guidance of **Dr. NOOR JAHAN** Professor, Department of Microbiology and Co-guide **Dr.SIRAJ AHMAD** Professor & Head Dept. of Comm. Medicine and **Dr. AUSAF AHMAD** Associate Professor, Department of Community Medicine, Integral Institute of Medical Sciences and Research, Lucknow.

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This is to certify that research work entitled **"Diagnostic and prognostic sepsis biomarkers in critical care patients - A systematic review"** submitted by **Pooja Yadav, Dr.Noor Jahan, Dr.Siraj Ahmad Dr.Ausaf Ahmad** for ethical approval before the Institutional Ethics Committee IIMS&R.

The above mentioned research work has been approved by Institutional Ethics Committee, IIMS&R with consensus in the meeting held on **19 May 2022**.

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DATE:15/07/2022 **POOJA YADAV**

DEDICATED TO

"TEACHERS"

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&

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CONTENTS

INTRODUCTION

Sepsis can be broadly defined as an organism's imbalanced immune response to an infection that ultimately damages its own organs or tissues. If this response is not detected at an early stage, it can lead to septic shock, that is, widespread inflammation throughout the body, which ultimately leads to multi-organ failure and death. There are more than 1.7 million cases of sepsis in the United States each year, and about 270,000 result in death. Also, of all deaths in hospitals, 1 in 3 is due to sepsis. Sepsis is also a leading cause of hospital readmission. [1]

Death from sepsis is not directly caused by invading microorganisms or pathogens; rather, the resulting clinical condition is caused by the dysregulation of the host's immune response leading to multiorgan dysfunction, coagulopathy and hypotension.

When an external pathogen invades, the host's defense system attempts to control foreign organisms from spreading and multiplying in the host body. This event is followed by an inflammatory response that activates the clotting process and the deposition of fibrin. However, during the overreaction of the immune system, this leads to a situation where clotting causes another diseased condition in a severe form leading to microvascular thrombosis and organ dysfunction, also known as disseminated intravascular coagulation (DIC).]

This microvascular thrombosis is an adaptive response to infection that prevents invading pathogens present in the tissues from spreading through the systemic circulation. So with this thrombosis, that is, by temporarily blocking the path between the tissue and the circulatory system, it prevents the entry of pathogens into the tissues of the body and in the meantime the immune system with the help of leukocytes removes pathogens or bacteria and repairs the tissues damaged. However, during acute infection, microvascular thrombosis is generalized, there is prolonged clotting, and extensive tissue ischemia (i.e., insufficient blood supply to an organ) can cause organ failure and death. This phenomenon is supported by studies of post mortem patients with sepsis, as they show the presence of microvascular thrombosis in

many organs, including the lungs, adrenal glands, liver, intestines, kidneys and even the brain.[4]

ROLE OF LYMPHOCYTES IN SEPSIS

A lymphocyte is a WBC subtype composed primarily of Natural Killer (NK) cells (24), T cells (thymus) (25), and B cells (bone marrow) (26). T lymphocytes are involved in cell-mediated immunity, i.e. they provide immunity by activating phagocytes, antigen-specific cytotoxic T lymphocytes, and release various cytokines in response to an antigen (foreign organism).

These lymphocytes along with dendritic cells (DCs) [6] become dysfunctional during sepsis. During sepsis, there is extensive apoptosis of T and B lymphocytes, accompanied by profound immunosuppression. [7] An increase in the number of suppressor T cells was also noted. Thus, for lethality associated with sepsis, it begins with apoptotic deletion of T and B lymphocytes followed by defective DCs, and this marks the onset of immunosuppression. Therefore, this faulty innate immune system leads to a loss of its ability to swallow bacteria, which equates to prolonged clotting and causes the development of multi-organ failure (MOF) and eventual death. Studies also show that the development of sepsis can also lead to redox imbalances in white blood cells (leukocytes) and organs due to the accumulation of reactive oxygen species (ROS). This is followed by an inflammatory response (SIRS), including a sustained immune response and other states of immune activation in endothelial cells and leukocytes.[8]

How common is sepsis and who gets it?

Very large epidemiological studies involving up to 6 million people give an incidence of 3 per 1000. Very few pathogens, apart from parasites like malaria, prefer to multiply in the blood. Thus, sepsis results from a violation of the integrity of the host barrier, physical or immunological, and the direct entry of the pathogen into the bloodstream, resulting in sepsis.[9]

The physical barriers to host invasion are formed externally by the skin and, contiguously internally, by the mucous membranes lining the gastrointestinal, urogenital and respiratory systems and the mucous membrane of the eye. Loss of outer barrier integrity is usually evident, although careless observers may miss more subtle ruptures formed by indwelling urinary catheters, intravenous cannulas, or endotracheal tube. Sometimes sepsis can result from seemingly insignificant interventions such as insect bites, thorn pricks, or minor skin abrasions. Loss of internal barrier integrity often occurs in the gastrointestinal tract, which extends from the mouth to the anus and includes the hepatobiliary system. Population per year or approximately 750,000 cases per year in the United States.[10]

Genetic studies looking for genes that confer vulnerability or protection have generally been too weak to provide anything other than suggestive evidence, or have yielded conflicting results.[11]

A lack of mannose-binding lectin due to mutations in the promoter or structural gene sequences that lead to functional or quantitative defects is associated with the development of sepsis, particularly pneumococcal sepsis.[12]

How to prevent sepsis?

The prevention of sepsis depends on the definition of the risk group and the availability of appropriate interventions. Invasive pneumococcal disease in agammaglobulinemic patients

has decreased since the advent of higher dose intravenous gammaglobulin. Vaccination to prevent sepsis has been validated for certain pathogens[13] and is limited to certain indications. Vaccines against pneumococcal, influenza H type B and meningococcal groups A and C are routine splenectomy prophylaxis, as in many countries against influenza H type B in children under 5 years of age and vaccine against meningococcal disease in adolescents. Pneumococcal bacteremia appears to be reduced in the vaccinated population.[14]

Maternal sepsis

Sepsis is an important cause of morbidity and mortality during pregnancy and the postpartum period; approximately 1 in 1000 women who give birth will develop sepsis, with half of these women progressing to severe sepsis and 3-4% developing septic shock.[15]

is a challenge in both resource-poor and resource-intensive environments; A quarter of women who die within 6 weeks of pregnancy in the UK die of sepsis. Globally, an estimated 11% of maternal deaths are caused by sepsis, with the vast majority occurring in developing regions. [16]

There are several recognized risk factors for maternal sepsis, including the presence of pre-existing medical conditions such as anemia, febrile illness within 2 weeks prior to the diagnosis of sepsis, and most importantly, the mode of delivery [17]. Cesarean section and operative vaginal delivery are associated with severe maternal sepsis [18]. The predominant causes of maternal sepsis vary by time of infection; before birth, urinary tract infections account for approximately one-third of all cases of maternal sepsis, while after birth one-third of sepsis are due to genital tract infections [18]. In general, infections due to E. coli are the most numerous, but group A Streptococcal infections are significantly associated with greater severity of sepsis [18]. There is good evidence that pregnant women are at increased risk of complications from certain specific infections, such as the flu, varicella zoster, and listeria.

Pregnant and postpartum women are generally young and fit and compensate well even with a severe infection [19]. Therefore, the infection may be well established before a diagnosis of sepsis is made. Early consideration of diagnosis and therefore early detection may therefore be even more important in the obstetrical population. It depends on both measuring vital signs in an ill pregnant or postpartum woman and acting on the results.[20]

Although pregnancy and childbirth are normal physiological processes, the presence of abnormal signs or symptoms cannot be considered normal. It is important to note that symptoms such as severe abdominal pain, shortness of breath, and diarrhea may accompany postpartum sepsis. In addition, maternal sepsis should always be considered as part of the differential diagnosis in a postpartum woman in shock. Although bleeding is the most common cause of shock in women after childbirth, possible sepsis should be investigated, especially when blood loss is moderate and treatment for bleeding seems ineffective. Regarding maternal shock.

It is important to be aware of the importance of having a group A streptococcal infection. Although caesarean section and operative vaginal birth are risk factors for maternal sepsis, group A streptococcal infections are proportionally more common in women who have delivered vaginally without assistance. Group A streptococcal infection is a known risk factor for the development of septic shock and is associated with rapid progression of sepsis.[21]

In a UK national study of severe maternal sepsis, 75% of women with group A streptococcal infection had less than 9 hours from the first signs of systemic inflammatory response syndrome to the diagnosis of severe sepsis [18]. For 50% of women, it was less than 2 hours. As with sepsis in the general population, the most important management action, along with early recognition and diagnosis, is to establish a package of sepsis care, including timely admin-

istration of antibiotics (within 1 hour of suspected sepsis), a adequate fluid resuscitation and whey measurement.

Pediatric sepsis

Adrienne G. Randolph Overwhelming infection is the leading cause of death in children worldwide [22]. Infants and young children are most at risk because their immature immune systems are less able to repel severe pathogens [23]. Sepsis - when a patient has a systemic inflammatory response to a suspected or confirmed infection [24] - is a useful construct because it must take the doctor to the bedside to examine the baby and determine the appropriate treatment. Children who develop signs of severe sepsis with organ dysfunction, and especially those who develop septic shock, are most at risk for life-threatening and life-threatening complications.

In recent years, the approach to the treatment of septic shock in pediatric patients has focused on the early detection of severe sepsis. This is followed by prompt treatment with antibiotics and aggressive treatment of shock with fluid boluses and, if refractory, vasoactive agents. These interventions, extrapolated from the treatment of septic adults, have been widely used as clinical guidelines [25]. Implementing these interventions as care packages with auditing and feedback can optimize clinical adherence. [26]

Although no large multicenter randomized trials have been conducted, there is evidence that implementing early detection of sepsis, prompt administration of antibiotics, and intravenous fluids have improved clinical outcomes. There is very strong evidence that attention to consistent adherence to the use of central line introducer and maintenance bundles can prevent nosocomial sepsis due to central line associated bloodstream infections [27]. Early detection of sepsis and aggressive treatment are necessary but not sufficient.

Treatment of “sepsis” should rapidly progress to a specific diagnosis with targeted antibi-

otic therapy against the bacterial, viral, fungal or protozoan pathogen. The most common infection in children is pneumonia, which is mainly caused by viral pathogens. Therefore, despite their widespread use, antibiotics are not effective for most children with a severe infection. With the exception of influenza, antivirals are also usually not indicated in immunocompetent hosts.

Rapid implementation of strategies to reduce antibiotic use is also not without risk. Children with life-threatening viral infections are often co-infected with highly pathogenic bacteria. In recent years, methicillin Staphylococcus aureus or resistant MRSA, which was relatively rare in children, has taken an increasing toll; MRSA flu is a particularly lethal combination. [28]

Sepsis in the pre-hospital setting

Patients with sepsis are usually transported to the emergency room via EMS [29]. These patients usually have more severe sepsis and higher mortality than those who present in other ways. As discussed in the previous sections, early identification and early treatment reduce the mortality and morbidity associated with sepsis.

With an average pre-hospital care interval of over 45 minutes for patients with sepsis, early intervention should take place in the pre-hospital setting. [30]

Introduction to the diagnosis of sepsis

The diagnosis of sepsis with traditional methods involves the process of culturing samples of blood, urine, cerebrospinal and bronchial fluid. In general, CRP or white blood cell counts serve as an indicator or clinical sign of sepsis. Blood cultures are performed in continuously monitored blood culture systems (CMBCS) and according to a set of pre-approved guidelines. [31]

Fully automated systems are common for blood sample incubation, along with the detection

and analysis of released CO2 and depleted O2 during the culture process. Detection is typically performed using fluorescent sensors commonly known as labeled detection techniques. In addition to labeled detection, there are several other techniques to estimate the level of released gases, including calorimetric analysis, automatic growth detection techniques, hybrid techniques including: the intrinsic fluorescence method of lysis centrifugation, the method intrinsic rapid fluorescence for rapid and direct identification of pathogens in blood cultures. [32]

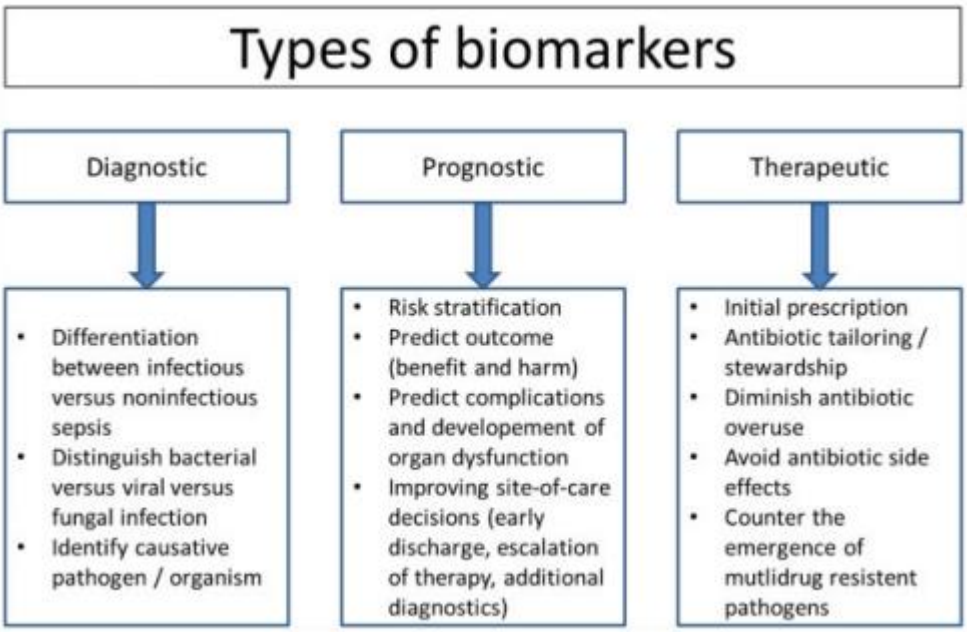
Among the traditional pathogen detection techniques, there are some relatively new detection schemes, including - multiplex PCR + hybridization or microarray, PCR + mass spectroscopy, broad spectrum PCR. These are mainly exercised on whole blood. Specialized techniques are now also used for the identification and susceptibility test of positive blood cultures. The use of techniques such as MALDI-TOF, Molecular POCT and their combination or Multiplexed PCR together with mass spectroscopy is used to increase the accuracy in the quantification of pathogens.

Biomarkers

Biomarkers can increase the accuracy of any bacterial presence and are useful for tracing the evolution of infectious processes. New biomarkers related to infectious diseases have been tested in recent years, but few have overcome the hurdles of rigorous testing for use in clinical practice [34]. Several biomarkers are already available for clinical use in sepsis; however, their effectiveness is in many cases limited by the lack of specificity and sensitivity. Other factors include the limitation to characterize the presence of infection and the complexity of inflammatory and immune processes to classify patients into homogeneous groups for spe-

cific treatments [35]. Many biomarkers can be used in sepsis, but none have sufficient specificity or sensitivity to be used routinely in clinical practice. PCT and CRP have been used most often, but even these have limited ability to distinguish sepsis from other inflammatory diseases or to predict outcome. Given the complexity of the sepsis response, it is unlikely that a single ideal biomarker will ever be found.[36] In the 1980s, many studies were conducted on C-reactive protein (CRP), an established member of the group of proteins synthesized in the liver. In the 1990s, researchers discovered that levels of procalcitonin (PCT), the precursor to the hormone calcitonin, were elevated in patients with bacterial infection.[37] Elevations in CRP and PCT were added to the updated definition of sepsis in 2003. Early in the last decade, clinical guidelines for intensive "targeted" treatment of severe sepsis and septic shock used levels lactate levels as a guide for therapy and maintaining a lactate level when monitoring patients at risk of developing sepsis has become standard practice.[38]

The term "biomarker" or "biological marker" refers to a medical condition observed from outside the patient that can be measured in an accurate, objective and reproducible way. This makes it any laboratory tool with the potential to better detect and characterize disease, simplify complex clinical algorithms, and improve clinical problem solving. From a clinical perspective, a biomarker should complement clinical judgment and interpretation of other diagnostic and prognostic tests and add information that ultimately improves patient care. An ideal biomarker should have fast kinetics and high sensitivity and specificity. Furthermore, it should be fully automatically identifiable, have short lead times and, at best, be available as a point-of-care test with low production costs. [39]


Types of biomarkers
Diagnostic
Prognostic
Therapeutic
• Differentiation between infectious versus noninfectious sepsis
• Distinguish bacterial versus viral versus fungal infection
• Identify causative pathogen / organism
• Risk stratification
• Predict outcome (benefit and harm)
• Predict complications and developement of organ dysfunction
• Improving site-of-care decisions (early discharge, escalation of therapy, additional diagnostics)
• Initial prescription
• Antibiotic tailoring / stewardship
• Diminish antibiotic overuse
• Avoid antibiotic side effects
• Counter the emergence of mutlidrug resistent pathogens

Review Of Literature

In a study by Denise Battaglini et. al 2022

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) causes a wide range of clinical manifestations, ranging from mild respiratory symptoms to pneumonia and, in more severe cases, multiple organ failure[40]. Mechanisms underlying multisystem involvement may include an imbalanced immune response that facilitates the progression of coronavirus disease 2019 (COVID-19). This hypothesis was confirmed by changes in laboratory biomarkers showing a greater potential for abnormal immune response, mainly an increase in the number of neutrophils and a significant decrease in the number of lymphocytes, altering the neutrophil/lymphocyte ratio. Such an abnormal immune response is driven by an increased serum concentration of many pro-inflammatory mediators. These include interleukin (IL) -1b, IL-2, IL-6, IL-8, interferon-induced protein 10 (IFN) -g, granulocyte colony stimulating factor, monocyte chemotactic protein 1 , the inflammatory macrophage protein-1a and among other tumor necrosis factor-a [41]. However, the inflammatory cytokine storm in patients with COVID-19 is less harmful than that seen in patients with sepsis or acute respiratory distress syndrome (ARDS), but without COVID-19 [42], raising questions about the mechanisms underlying the multiorgan involvement in COVID-19.

ROLE OF BIOMARKERS IN THE RESPIRATORY SYSTEM

The lungs are usually the organs most affected by SARS-CoV2, due to their large, highly vascular surface. [43] The pathogenesis of COVID-19 in the lungs involves an initial phase of local inflammation, endothelial cell damage, and antifibrinolytic activation in the upper and lower respiratory tract, followed by repair mechanisms that can trigger the restoration of normal lung architecture. Inflammation is followed by recruitment of platelets with degranulation,

clot formation, impaired vascular permeability and accumulation of leukocytes at the injury site, leading to the recruitment of other inflammatory cells with the involvement of specific cytokines (i.e., IL-4, IL- 13, transforming growth factor-b) which are also responsible for pro-fibrotic activity. [44]

In the early course of the disease, neuron-specific enolase (NSE) can be used to distinguish patients who will develop dyspnea. On admission, higher lymphocyte and platelet counts and lower ferritin, D-dimer, lactate dehydrogenase (LDH), and aspartate transaminase (AST) were all associated with a lower risk of death in COVID-19 patients who eventually required intubation and mechanical ventilation. 45]. Levels of surfactant protein-D, angiopoietin-2, trigger receptors expressed on myeloid cells (TREM)-1 and TREM-2 were found to be higher in mild/moderate and severe COVID-19 pneumonia /critical only in asymptomatic and uncomplicated cases. Moreover, these biomarkers correlated well with clinical severity.[46] In severe cases of COVID-19, total thiol, ferritin and LDH have been identified as prognostic biomarkers for the development of ARDS. COVID-19 survivors had higher platelet counts and neutrophil to lymphocyte ratios and lower C-reactive protein (CRP), D-dimers, ferritin, LDH and AST.[47]

CARDIOVASCULAR SYSTEM

SARS-CoV-2 can directly trigger endothelial dysfunction and cause a condition known as COVID-19-associated coagulopathy. After viral entry into cells, increased vascular permeability and tissue factor expression in subendothelial cells with activation of platelets and leukocytes can trigger the coagulation cascade. Endothelial damage and a generalized inflammatory state are factors of thrombosis, which can contribute to cardiovascular manifestations.[48] Acute heart failure and exacerbation of chronic heart failure are reported in up to 20-30% of hospitalized patients and result in high mortality rates, particularly in patients with severe

comorbidities.[49] Recent evidence has confirmed that cardiac biomarkers, including natriuretic peptides (NPs) and troponins, may reflect cardiovascular involvement and inflammation in COVID-19 and are strongly associated with poor prognosis and mortality Other cardiac and non-cardiac biomarkers are common findings in COVID-19-associated cardiovascular disease, including creatine kinase (CK)-MB, myoglobin, D-dimer, brain natriuretic peptide (BNP) and its N-terminal pro-hormone (NT-proBNP), and neutrophil-to lymphocyte ratio[50] Myoglobin seems to offer higher prognostic precision in COVID-19 than other cardiac biomarkers (troponins and CK-MB). In addition, it has been found that the pro-adrenodullinde (MR-Proadm) mirror (MR-Proadm) mederégional with endothelial dysfunction and mortality in the COVID-19 is associated, which can be an optimal biomarker to predict survival in this population of patients. [51]

Coagulation in hemostasis

Management coagulation is a well-known systemic effect of COVID-19, which can come from direct or indirect viral influences on endothelium or immunoshade. [52] The COVID-19 can cause changes in the coagulation cascade to cause coagulation and fibrinolysis regulation mechanisms, changing the function of thrombocytes and hyper-inflammatory reaction. [53] In this context, the D-Dimer was identified among the first coagulation biomarkers modified in COVID-19 and mortality is provided for approval. Likewise, plasma fibrinogen seems to be linked to hyperinflammation and the severity of the disease in the COVID-19 [54]. A coagulopathy diagnosis of COVID-19 coagulopathy has been identified, in particular an increased mirror of the adhesion molecule of soluble vascular cells (SVCAM) -1, by the Willebrand factor (VWF), thrombomodulin, Soluble tumor necrosis factor (TNF) receptor I (sTNFRI), Heparin Sulfate, C5B9 complement, plasminogen-activator inhibitor (PAI) -1 and antiplasmin alpha2 among others. [55]

Neurological participation

Although COVID-19 rarely influences the brain as a primary manifestation, neurological complications in this population of patients are common. [56] Patients with neurological complications compared to patients can occur more stays in the hospital, and the duration of mechanical ventilation can be associated with the risk of developing new neurological complications. [57] Imaging of magnetic resonance and magnetic resonance (MRI) is considered to be the ordeal for the detection of brain disturbances, although the use of methods which are exposed to ionizing radiation in the case of non Mainly in brain injured patients are only high -suspected neurological. Complications can be justified. [58] The use of multimodal neuromonitoring has received more and more attention as a means of identifying patients with a higher risk of cerebral strengthening, as low costs, speed, safety and preparation respect availability . However, the use of neuromonitoring tools is still mainly limited to specific settings (eg, intensive care) and patient populations. [59]

Unlike imaging, blood biomarkers can detect brain damage and efficiently predict prognosis. Blood biomarkers for studying brain disorders include glial fibrillar acid protein (GFAP), neurofilament light polypeptide (NfL), tau, calcium-binding protein S100B, NSE, and inflammatory markers. Increased GFAP staining was found in post mortem brain tissue analysis of COVID-19 patients [60] and NfL was significantly associated with COVID-19 status. [61] Another study reported that GFAP was elevated in both moderate and severe COVID-19 cases, while serum NfL was elevated only in severe cases compared with controls. Inflammatory and coagulation markers such as D-dimer, LDH, erythrocyte sedimentation rate (ESR) and CRP have been independently associated with the onset of ischemic stroke in

COVID-19, while advanced age, diabetes mellitus and hypertension are not results are significant predictors of stroke in these patients, despite being known predictors of non-COVID-19 stroke. Levels of lymphocytes, procalcitonin, and creatinine were higher in stroke patients with COVID-19. [61]

KIDNEY AND LIVER

COVID-19 can cause kidney and liver damage through direct cell infection, through host immune clearance and immune tolerance disturbances, endothelium-associated vasculitis, thrombus formation, metabolic and glucose disturbances, or hypoxia tissue. Consequently, biomarkers of endothelial, renal, hepatic, vascular, or hypoxic damage can help detect new organ involvement and help determine prognosis. [62] About 25% of hospitalized patients with COVID-19 reportedly developed acute kidney injury, including low molecular weight proteinuria, Fanconi syndrome, and tubular damage. [63]

New urinary biomarkers have been proposed in COVID-19, including levels of 11-dehydrothromboxane B2, 8-hydroxy-2′-deoxyguanosine and liver-type fatty acid binding protein (LFABP), all of which were higher in this patient. . cohort at admission [64]. N-acetyl-b-D-glucosaminidase, b2-microglobulin, 1-microglobulin and L-FABP, all of which are markers of tubular damage, were significantly associated with inflammation, as were IL-6 levels [65]. Indeed, another observational study confirmed the association between pro-inflammatory cytokines, urinary cytokines and markers of renal damage in urine [66]. Procalcitonin was associated with acute kidney injury in COVID-19, and a score containing simple and easily accessible variables such as procalcitonin, arterial oxygen saturation and blood urea nitrogen predicted acute kidney injury. [67]

In a study by Vanessa Catenacci et. al 2022

With 48.9 million cases of sepsis and 11 million sepsis-related deaths in 2017, the disease has a mortality rate of around 22% and accounts for 19.7% of deaths worldwide [68]. In order to combat the high mortality rate, the surviving septicemia campaign highlights the importance of early therapeutic interventions and improved screening in high -risk patients. [69] The presentation of sepsis and the result are influenced by several factors, including the characteristics of patients, causal micro-organism and infection. [69] While the current Sepsis-3 definition uses the Sequential Organ Failure Assessment (SOFA) scale to diagnose patients, the use of a highly specific and sensitive diagnostic biomarker could aid timely and appropriate treatment. In addition, the use of SOFA and quick SOFA (qSOFA), as risk stratification models, is limited by low specifcity, and the sensitivity and specifcity of qSOFA have been shown to vary widely across studies.[70]

The identification of an ideal biomarker for septicemia is a challenge due to the complex intersection between the pro-coagulated, pro-inflammatory and anti-inflammatory mechanisms in the pathology of sepsis. [71] An example of such a biomarker is protein C (PC), activated protein C cyrogen (APC). The APC is a glycoprotein dependent on vitamin K which circulates through blood plasma. [72] APC mainly called anticoagulans, the coagulation cascade regulates negatively by preventing the formation of fibrin and activation of platelets and coagulation by inhibiting factor V and VIII. [73] It also contributes to anti-inflammatory inflammation by high regulation of anti-inflammatory mediators, control of the dangerous associated associated molecular patterns and the regulation of the adhesion and migration of leukocytes. [74] In sepsis, the deregulation of the PC contributes to excessive thrombosis and inflammation. [75]

In a study on Zobeida Cruz-Monserate and. al 2021

Biomarkers are objective measures that can be indicators of normal biological or pathogenic processes or reactions in relation to therapeutic interventions for a certain disease. [76] So

far, there is no reliable diagnostic, prognostic or therapeutic biomarker for chronic pancreatitis (CP). [77] The CP is characterized by chronic inflammation and progressive fibrosis of the pancreas, with the loss of ad cellular mass. This leads to irreversible morphological changes, the loss of pancreatic function and an increased risk of pancreatic cancer. [78] The development of precise prognostic prognostic biomarkers could develop CP complications in final stages such as diabetes, exocrine insufficiency, bone diseases or pancreatic cancer which facilitates the development of blocking strategies, delays or slow diseases. [79] Consequently, the lack of development of successful biomarkers in CP research has been a difficult objective for decades and represents an important research gap in our knowledge. Among biofluids and tissue biomarkers, we identified 30 potential biomarkers with a moderate effect size and five potential biomarkers with a large effect size. [80]

Adenosine

Adenosine is a metabolite of ATP hydrolysis and as such increases the metabolic stress caused by the disease. In CP patients, adenosine levels in urine were significantly elevated compared to healthy controls in a study comparing urinary metabolomics using a 1H-NMR (proton nuclear magnetic resonance) test. [81]

Adiponectin

Adiponectin is an anti-inflammatory adipokine secreted primarily by adipocytes and may reduce the secretion of many proinflammatory cytokines.44 However, the adiponectin data examined had mixed results; that is, in terms of distinguishing between CP and healthy controls, adiponectin was found to be ineffective in some studies. [82]

Des-Leu albumin

Des-Leu albumin is a truncated form of serum albumin devoid of the C-terminal leucine residue, possibly due to the action of pancreatic carboxypeptidase-A. The des-Leu form of albumin

was found to comprise 68% of circulating albumin in hospitalized patients with CP versus 5% in control patients. [83]

Interleukin 6 (IL-6)

IL-6 is a pro-inflammatory cytokine produced by many cell types, including macrophages and adipocytes. IL-6 levels are often elevated due to infections, acute or chronic inflammation, and cancer. [84]

In a study by Georgios D. Kitsios et. al 2020

Dysregulation of innate immunity is a central pathogenetic feature of the heterogeneous syndromes of sepsis and acute respiratory distress syndrome (ARDS) [85]. In several independent populations, patients with high systemic levels of inflammatory cytokines and biomarkers of tissue damage (classified as a hyperinflammatory subphenotype) show worse organ dysfunction and clinical outcomes than their hypoinflammatory counterparts. [86] Many of the predictive biomarkers for the damaging hyperinflammatory subphenotype (e.g. IL-6 and IL-8, soluble TNFR1, procalcitonin, and receptor for advanced glycation end products [87] reflect the canonical pathways of immune cell stimulation by part of pathogens and molecular patterns associated with damage (PAMP and DAMP, respectively [88]. PAMPs include microbial nucleic acids as well as cell wall components such as LPS from gram-negative bacteria and fungal 1-3-β-d-glucan (BDG).[89]

In mechanically ventilated immunocompromised patients, airway colonization with Candida species indicates poorer outcome.[90] In patients suspected of having ventilator-associated pneumonia, Candida species in airway secretions have been associated with increased levels of IL-6 and procalcitonin and increased mortality.[91] Overgrowth of C. albicans in the human intestine occurs in the setting of sepsis treated with antibiotics, which increases the risk of secondary candidemia.[92] Dysregulation of host responses with elevated levels of cir-

culating inflammatory cytokines and immune cell activation is an important pathogenetic feature in the development of critical diseases. Unsupervised staging analyzes in patients with sepsis, severe pneumonia, or ARDS have revealed the presence of distinct subphenotypes characterized by a cluster of hyperinflammatory versus hypoinflammatory host responses.[93] We observed associations of circulating BDG with innate immune responses as well as biomarkers of epithelial permeability. BDG can stimulate innate immunity not only through mucosal interactions, but also in the bloodstream and in the reticuloendothelial system.[94] We further showed that the magnitude of the systemic inflammatory response (represented by ST-2) varies depending on the dectin-1 receptor genotype and that BDG in these patient samples was also able to stimulate the dectin-1 receptor. dectin-1 in a journalist. in vitro cellular system. Therefore, circulating BDG molecules may not only be a marker of a breach in the mucosal barrier that has found its way into the bloodstream, but also an active mediator of inflammatory organ dysfunction and disease severity. .[95]

In a study by Esther Nkuipou-Kenfack et.al (2020)

In high- and middle-income countries, millions of patients survive critical illness thanks to highly specialized life-sustaining management in intensive care units (ICUs). However, the cumulative mortality during the first year after leaving the ICU ranges from 26 to 63%. [96]. Urine proteomic profiling has emerged over the past 15 years as a breakthrough technology that enables the discovery of disease-specific, multidimensional biomarkers indicative of molecular pathogenic processes.[97]

In a study by Rupali Patnaik et.al (2020)

Neutrophil surface receptors recognize the bacterial antigen and thereby activate neutrophils. Activated neutrophils have the capacity for phagocytosis, chemotaxis, oxidative burst, and cytokine production.[98] Phagocytosis is facilitated by various opsonins such as immunoglobulin G (IgG) and complement factors. Polymorphonuclear leukocytes (PMNs) express receptors

for IgG opsonin binding, called Fcγ receptors. These receptors are called Fcγ receptors because they bind to a specific part of the antibody called the Fc region (constant region). Differentiation Cluster 64 (CD64) is the monoclonal antibody that recognizes the neutrophil receptor FcγR1. To distinguish sepsis from non-sepsis, a cutoff CD64 index of 1.66 showed sensitivity of 100%, specificity of 95%, positive predictive value (PPV) of 96%, and predictive value negative (VPN) of 95%. To distinguish sepsis from non-sepsis, a cutoff CD64 index of 1.66 showed sensitivity of 100%, specificity of 95%, positive predictive value (PPV) of 96%, and predictive value negative (VPN) of 95% . Previous studies have described CD64 expression to be higher in patients with Gram-negative infection.[99]

In a study by Wenping Zhang et.al (2019)

In developed countries, the incidence of sepsis reaches 100/100,000[100] and approximately 2% of hospitalized patients are diagnosed upon admission.[101] MicroRNAs (miRNAs) are small endogenous non-coding RNAs approximately 21-25 nucleotides in length. In 1993, Lee [6] discovered the first miRNAs (lin-4) miRNAs in new species of Caenorhabditis. Since then, thousands of miRNAs have been discovered. MiRNAs can inhibit post-transcriptional gene expression or promote targeted mRNA degradation, but they cannot code for a protein. MiRNAs can be detected in a variety of fluids, such as blood, sweat, and urine. Whole panels of deregulated miRNAs have been described in the blood of patients with inflammatory / infectious diseases, suggesting that circulating miRNAs may be suitable biomarkers in sepsis. [102] miRNAs have been used as biomarkers for various cancers since the discovery of circulating miRNAs in human peripheral sera. Several circulating miRNAs have been identified as potential biomarkers for sepsis, but their role in infectious diseases has rarely been studied. [103] It has been reported that miR-150 plasma can be used as a serum biomarker to diagnose patients with sepsis. The expression profiles of miR-150, miR-182, miR-342-5p and miR-486

were used to distinguish sepsis patients from healthy controls by genome-wide miRNA profiling using microarray analysis of eight peripheral blood leukocytes. individuals and eight patients with sepsis. [104] In this study, miR-223-3p was highly expressed in the circulating blood of patients with sepsis secondary to pneumonia. Wang et al. compared miR-223 levels in 50 patients with sepsis, patients with systemic inflammatory response syndrome (SIRS) and healthy controls. The expression level of miR-223 is increased in the blood of patients with sepsis and SIRS caused by infection, but not in the blood of patients with non-infectious SIRS. [105]

In a study by Jinle Lin et. al of 2018

Acute respiratory distress syndrome (ARDS), characterized by permeable pulmonary edema and refractory hypoxemia, has a dramatic impact on morbidity and mortality.[106] Biomarkers, which are often measured objectively and not influenced by personal interpretation, can facilitate rapid diagnosis and risk stratification of ARDS. Although various biomarkers such as surfactant protein D (SP-D), soluble receptor for advanced glycation end products (sRAGE) and lung cancer (KL-6) have been studied for potential use in the diagnosis of ARDS, their clinical utility is not limited due to lack of distinctiveness.[107] Club cell protein (CC16), an anti-inflammatory protein primarily produced and secreted by club cells in the distal respiratory or terminal bronchioles, has been proposed as a biomarker of lung epithelial damage.[108] Given the large blood-tissue exchange surface of lung tissue, CC16 serum is almost exclusively derived from the respiratory tract and is therefore considered lung-specific. Elevated circulating levels of CC16 have been observed in patients with lung damage caused by inhalation of ozone, chlorine and LPS.[109] It has been proposed as a disease marker for pulmonary sarcoidosis, chronic obstructive pulmonary disease, and severe chest trauma.[110] However, it is unknown whether CC16 levels can be used in the diagnosis, clas-

sification, and prediction of ARDS outcomes, although some clinical studies suggest that circulating CC16 levels are associated with the development of ARDS.[111] Elevations in serum or plasma CC16 levels have been documented in studies of lung injury caused by multiple etiologies, including systemic sclerosis, mechanical ventilation, air pollution, pulmonary sarcoidosis, and lung transplantation.[112] This study confirms that CC16 could be used as an effective diagnostic marker for ARDS. Our results showed that CC16 is an independent factor that can facilitate the diagnosis. Statistically discriminated CC16 values greater than 33.3 ng/mL discriminate between ARDS and non-ARDS patients, demonstrating relatively high diagnostic accuracy. Although we did not compare the diagnostic value of CC16 to other biomarkers in this study, previous studies have shown that CC16 has greater diagnostic ability than surfactant protein-D (SP-D), lung cancer-6 (KL-6), and soluble receptor for advanced glycation end products (sRAGE) for ARDS.[113]

In a study by Marco Bo Hansen et. al of 2016

Necrotizing soft tissue infection (NSTI) is a bacterial infection of any layer of the soft tissue compartments that is associated with necrosis. The condition is often accompanied by septic shock and the generalized inflammatory response is considered a major cause of death.[114] Delaying surgery has been shown to be an independent risk factor for mortality, and studies emphasize the importance of surgical debridement and early amputation of infected limbs.[115] Biomarkers can provide treatment guidelines and prognosis, thereby improving decision-making in patients with NSTI. To date, C-reactive protein (CRP) and procalcitonin (PCT) have been used to monitor the progression of infectious diseases in the intensive care unit (ICU).[115]

Pentraxin-3 (PTX3) is a multifunctional pattern recognition molecule released at the onset of

inflammation as part of the innate immune system by activating classical and lectin complement pathways through the specific recognition of C1q, lectin mannose-binding, ficolin-1 and ficolin-2 subunits.[116] An elevated level of PTX3 is associated with disease severity and mortality in patients with myocardial infarction [117], ischemic stroke, cancer, acute respiratory distress syndrome, and sepsis. [118] PTX3 is closely related to CRP as both are members of the pentraxin family of proteins, and PTX3 is central to antimicrobial responses and clearance of cellular debris. Since PTX3 is produced locally by various cells, including monocytes, neutrophils, and endothelial cells, in response to tumor necrosis factor and bacterial products, it is reasonable to consider PTX3 as a marker of local inflammation. , detected by direct release into the bloodstream. 119] In contrast, CRP is produced in the liver in response to locally induced interleukin-6, while PCT expression and synthesis in response to inflammatory stimuli appears to be more pervasive.[120]

In a study by Beata Mickiewicz et. al of 2015

In children ≥ 1 year old, sepsis is the second leading cause of death in the United States.[121] The frequency of sepsis in children is increasing. Researchers in one study found an 81% increase in hospitalizations for severe sepsis between 1995 and 2005.[122] Additionally, sepsis can cause significant physical, neuropsychological, and neurocognitive morbidity in survivors. For example, in a recent multicenter study, researchers found that 34% of survivors of severe sepsis had deteriorating functional status at 28 days, and 18% had a "poor" functional outcome (moderate, severe, or vegetative).).).[123] The vast majority (>80%) of children requiring emergency care present to an emergency department that does not have this specialized pediatric expertise. This problem has generated “great interest in the development of diagnostic and stratifying biomarkers of sepsis. A systems biology approach to phenotyping biomarkers of systemic response to sepsis has the potential to provide diagnostic and patient stratification profiles that inform clinical decision making.

In a study by James M O'Brien et. al 2005

The authors estimate an incidence of severe sepsis at 0.54 cases / 1000 population per year, indicating that severe sepsis is responsible for 0.61% of all hospital admissions and 11% of all ICU admissions. in the Netherlands. [125] The mortality rates of patients with systemic inflammatory response syndrome, sepsis, severe sepsis and septic shock were 24.2%, 33.9%, 46.9% and 52.2%, respectively [126].

They examined the colonization and transmission rate of coagulase-negative staphylococci in 20 intubated patients. On at least one occasion, 85% of subjects were colonized with coagulase-negative staphylococci and 70% appeared to be involved in at least one coagulase-negative staphylococcal transfer event. [127] a patient with postoperative Pseudomonas meningitis with serial They examined the rate of colonization and transmission of coagulase-negative staphylococci in 20 intubated patients. At least once, 85% of subjects were colonized with coagulase-negative staphylococci, and 70% appeared to have been involved in at least one coagulase-negative staphylococcal transmission event.[127] a patient with postoperative meningitis due to Pseudomonas with serial studies of cerebrospinal fluid from the ventricular and lumbar drains. Lumbar inflammation was consistently greater (higher leukocyte count, higher protein, and lower glucose) than seen with ventricular drains. The authors suggested that diagnosis based on ventricular cerebrospinal fluid could lead to delays in detection.[128]

Procalcitonin and C-reactive protein could distinguish between patients with and without bacterial infections. Among patients admitted with suspected infection, procalcitonin was significantly higher in patients with bacteremia and septic shock. However, procalcitonin did not distinguish patients with less severe infections from those without. C-reactive protein did not provide information about the severity of infection, but differentiated between infected and uninfected people.

AIM AND OBJECTIVES:

AIM -

To determine diagnostics and prognostics sepsis biomarkers in critically care patients

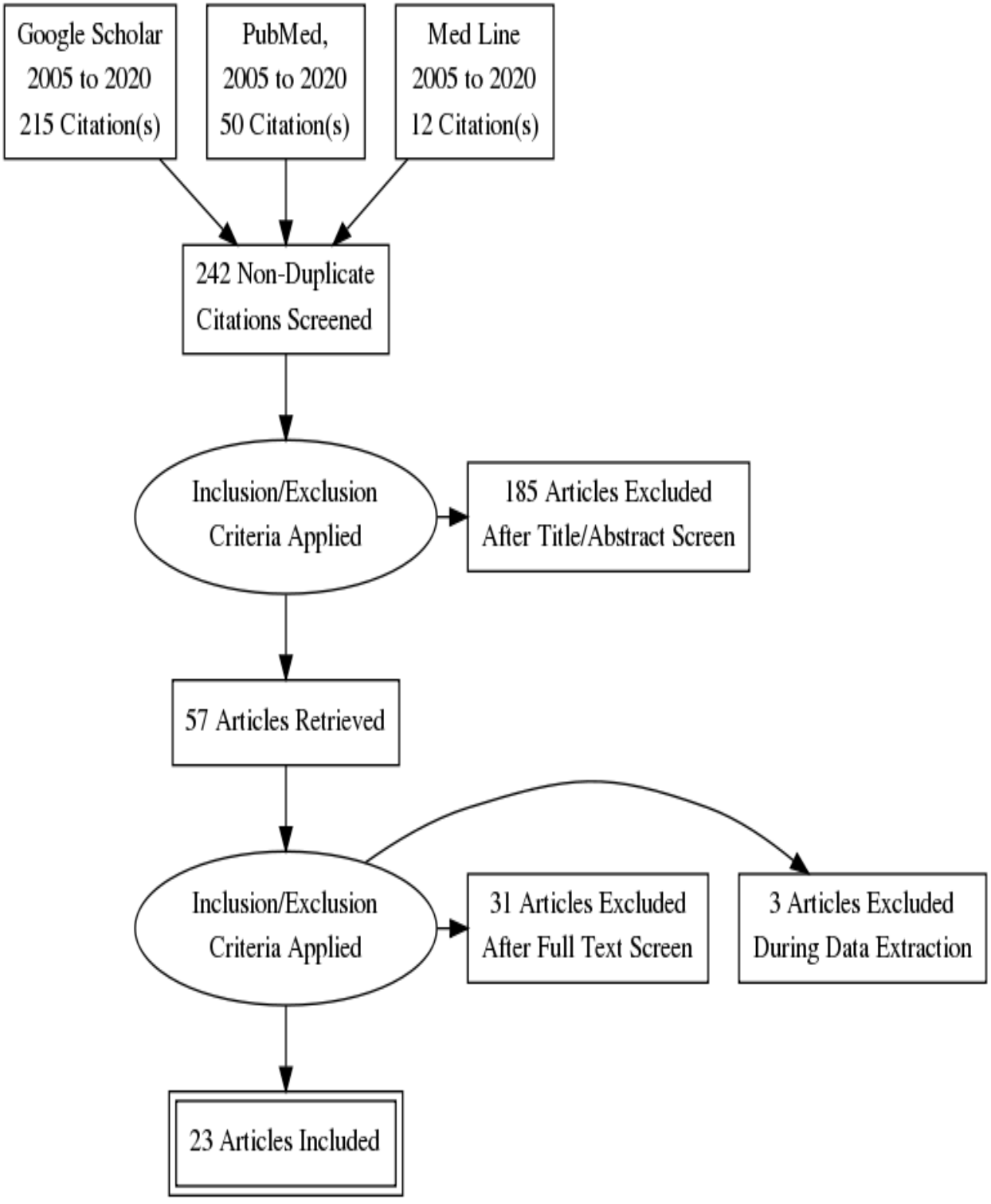
OBJECTIVE – To detect biomarkers in septic patients

STUDY METHODOLOGY

STUDY DESIGN

SYSTAMATIC REVIEW STUDY

STUDY SOURCE – Pubmed, google scholar , Cochrane library and research gate data base.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12 Citation(s)
242 Non-Duplicate
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Inclusion/Exclusion
Criteria Applied
185 Articles Excluded
After Title/Abstract Screen
57 Articles Retrieved
Inclusion/Exclusion
Criteria Applied
31 Articles Excluded
After Full Text Screen
3 Articles Excluded
During Data Extraction
23 Articles Included

RESULT

S.NO.	AUTHOR	YEAR	PLACE	FINDING
1.	Denise Battaglini et.al	2022	China	NSE,AST,LDH,MB,D-Dimer,Neutrophil count,troponins,myoglobins biomarkers used to predict disease severity in covid patients
2.	Vanessa catenaccio et.al	2022	Canada	Protein C levels were less reduced in sepsis survivors compare to non survivor and less reduced in septic patients without DIC as compared to those with DIC.
3.	Zobeida Cruz-Monserrate et.al	2021	Colombus	5 biomarkers had a large effect size whereas 30 biomarkers had a moderate effect size for distinguishing CP cases from other diseases
4.	Georgios D et.al	2020	USA	Patients with ARF had hire BDG levels where as patients with ARF with high BDG levels had HIRE odds for assignment to prognostically adverse hyper inflammatory sub phenotype
5.	Esther Nkuipou-kenfack et.al	2020	Belgium	Urinary proteomic classifier ACM128 predicts 1 year post ICU mortality over and beyond clinical risk factor
6.	Rupali Patnaik et.al	2020	Lucknow	nCD64 is a highly sensitive and specific marker for diagnosis of sepsis

7.	Wenping Zhang et.al	2019	China	miRNA chip technology was applied to identify miRNAs in the plasma of patients with pneumonia
8.	Jinle Lin et.al	2018	China	serum CC16 levels in ARDS patients were higher in non ARDS patients .sensitivity, specificity,positive predictive value were 90.4%,79.8%,74.2% respec-tively
9.	Marco vo Hansen et.al	2016	Denmark	Patients with NSTI were in-cluded over 25 months with up to 2.5 year followup,71% had septic shock, amputation in 20% and mortality was 27% plasma PTX3 level was higher in septic shock pa-tients
10.	Beata Mickiewicz et.al	2015	Canada	94 PICU sepsis , 81 ED sep-sis and 63 ED control patients were included
11.	James MO Brien et.al	2005	USA	Incidence of severe sepsis of 0.54 cases /1000 population /year from which 0.61% of hospital admissions and 11% of ICU admission

DISCUSSION

Sepsis is a life threatening organ dysfunction.early diagnosis in the cornerstone of sepsis care.Biomarkers play an important role in sepsis for diagnosis and treatmentHere we have discussed about several biomarkers which are indicators for many critical illness .Protein C biomarker increases in the DIC (disseminated intravascular coagulation).Thirty five biomarkers with different effect sizes helps to distinguish chronic pancreatitis.Plasma 1,3-beta-D glucagon level predict the fungal infections.Some novel urinary biomarkers are discussed the diagnosis of kidney diseases.Neutrophil CD-64 is discussed which have a better diagnostic value in sepsis.Some other biomarkers like microRNAs, Club Cells Protein16(CC16),Pentraxin-3 etc. are discussed for the diagnosis and prognosis of sepsis .

CONCLUSION

- Laboratory biomarkers have shown significant diagnostic and prognostic value in COVID-19 patients.
- Biomarker like protein C are useful in detection of Disseminated intravascular coagulation.
- Adenosine, adinopectin, interleukins help to diagnose chronic pancreatitis.
- BDG measurements offered prognostic information in critically ill patients without fungal infections.
- Neutrophil CD64 is a useful diagnostic and prognostic biomarker of sepsis
- MiR-223-3p could be used to predict pediatric sepsis
- CC16 useful for ARDS.
- Pentraxin-3 associated with septic shock ,amputation or death

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