

General Surgery

A Focus on Intra-Abdominal Sepsis with Biomarkers: A Literature Review

Rıfat Peksöz^{ID}, Enes Ağırman^{ID}, Fuat Şentürk^{ID}, Yavuz Albayrak^{ID}, Sabri Selçuk Atamanalp^{ID}

ABSTRACT

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection according to the Third International Consensus Definitions for Sepsis and Septic Shock definitions. It is a clinical condition with high morbidity and mortality due to its complex pathophysiology and lack of a complete treatment. It constitutes a significant economic burden because it constitutes a substantial part of intensive care patients, and the treatment process is lengthy and costly. Therefore, early diagnosis and treatment of the disease are essential.

After pneumonia, an essential source of sepsis is intra-abdominal infection. Due to the presence of multiple and polymicrobial sources of infection, abdominal sepsis progresses more seriously. The effective treatment of intra-abdominal infection consists of early recognition of the disease, control of the source, appropriate antibiotic therapy, and stabilization in the intensive care setting with an excellent surgical approach.

We searched PubMed, EMBASE, MEDLINE, and the Cochrane Library. Two authors reviewed all identified abstracts and selected articles for full-text review. We included original studies assessing mediators in intra-abdominal sepsis.

Inflammatory and protein mediators such as acute phase protein and chemokine cytokines play an essential role in intra-abdominal sepsis. In clinical practice, white blood cell count, C-reactive protein, and procalcitonin are the most used parameters in the definition of abdominal infection. Tumor necrosis factor-alpha, interleukin-6, high-mobility group protein B1, and presepsin are other markers with high diagnostic efficiency, even though they are not used routinely. Despite everything, there is a need for highly effective markers that can be used in the diagnosis and follow-up of sepsis. Great hope is attached to these markers.

This review aims to discuss the importance of the most used markers in the diagnosis and follow-up of abdominal sepsis and the markers on which there are essential studies in light of current literature.

Keywords: Intra-abdominal infection, biomarkers, inflammatory mediators, sepsis-3

Introduction

At the present time, the rate of septic diseases is increasing rapidly due to the increasing elderly population. Considering the patients with suspected sepsis but not registered, the actual rate is higher than reported in the literature. Despite advances in all diagnostic and treatment modalities, sepsis remains the leading cause of death in surgical intensive care units. It creates a severe economic burden due to the complex and long-term treatment. Therefore, early diagnosis and treatment of the disease are essential.¹⁻⁴

According to previous definitions, sepsis has been defined as a systemic inflammatory response syndrome (SIRS) against infection. It was called severe sepsis when organ failure was added and septic shock when cardiocirculatory failure was added to SIRS.⁵ However, due to the deficiencies in these definitions, the sepsis criteria were revised in the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) in February 2016. The use of the SIRS criteria and the definition of severe sepsis have been abandoned in this consensus. Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection according to sepsis-3 definitions. According to this classification, a Sequential Organ Failure Assessment

Cite this article as: Peksöz R, Ağırman E, Şentürk F, Albayrak Y, Atamanalp SS. A focus on intra-abdominal sepsis with biomarkers: A literature review. *Eurasian J Med*, 2022;54(Suppl. 1), S66-S70.

Department of General Surgery, Atatürk University Faculty of Medicine, Erzurum, Turkey

Received: September 2, 2022

Accepted: November 15, 2022

Publication Date: December 1, 2022

Corresponding author: Rıfat Peksöz

E-mail: rifat-peksöz@hotmail.com

DOI 10.5152/eurasianjmed.2022.22296



Content of this journal is licensed under a Creative Commons Attribution 4.0 International License.

(SOFA) score of ≥ 2 points due to intra-abdominal infection (IAI) was considered abdominal sepsis.⁶ In determining the bedside sepsis-related prognosis in adult patients with suspected disease in the out-of-hospital, emergency room, or general hospital conditions, quick SOFA can be used. Quick SOFA uses these 3 criteria: hypotension, altered mental status, and tachypnea.⁷

Septic shock is the presence of sepsis with (despite adequate volume resuscitation) the persistent hypotension-requiring vasopressor drugs to maintain mean arterial pressure ≥ 65 mm Hg and lactate level ≥ 2 mmol/L. Mortality in these patients is over 40%. Hypoperfusion in sepsis impairs tissue perfusion and microcirculation. Changes in metabolism cause lactic acidosis, oliguria, and changes in mental status. These changes herald the development of multiple organ dysfunction syndromes.^{6,7}

Intra-abdominal infection is the second most common cause of sepsis after pulmonary focus.⁸ Intra-abdominal infections are separated into 2 parts, uncomplicated or complicated, according to the width of the infection. An uncomplicated IAI rarely causes a critical illness with organ failure. On the other hand, complicated IAI caused by disruption of the gastrointestinal tract or other hollow organs causes localized or diffuse peritonitis. This causes organ failure and, ultimately, abdominal sepsis. Abdominal sepsis may occur due to spontaneous perforation (e.g., gastric ulcer perforation), complicated diverticulitis, or complication of elective abdominal surgery. Intestinal perforation and other surgical complications arise after surgery, especially in a significant portion of the patients in the surgical intensive care unit.^{3,9,10} Complicated IAI represents the second most common cause of infectious morbidity and mortality after pneumonia.¹¹ Sixty-six percent of surgical sepsis patients are due to IAI. The mortality of abdominal sepsis varies between 7.6% and 36%. Again, the

majority of surgical patients occur after elective surgery.¹⁻³

The increase in the number of IAI patients continues. The disease becomes more fatal due to multiple and polymicrobial sources of infection.¹² Effective treatment of IAI consists of early recognition of the disease, control of the source, appropriate antibiotic treatment, and stabilization in the intensive care setting with a good surgical approach.¹³ To better understand the pathogenesis and management of intra-abdominal sepsis, many experimental studies have been conducted and continue to be conducted on polymicrobial sepsis generation and preventive treatment.¹⁴⁻¹⁸

Sepsis is the interaction between the host and pathogens. In this effect, biochemical mediators are produced, and inflammatory cascades are triggered.¹⁹ The pathogenesis of sepsis involves the activation and release of stress hormones, hundreds of mediator molecules, cytokines, and acute phase proteins, which can be considered prognostic biomarkers.²⁰

Early diagnosis and timely treatment will improve the results of the disease. Thus, a method that can diagnose sepsis in the early phase, make an early prognostic evaluation, and fully determine the effectiveness of treatment and surgical management gains vital importance. Great hope has been placed on biomarkers as a method to cope with these problems.¹¹

This review article aims to investigate the significance of inflammatory mediators for abdominal sepsis. Again, we discussed the value of these mediators in the early diagnosis of intra-abdominal sepsis and their significance in not predicting the outcome of the disease in light of current literature.

Methods

We searched PubMed, EMBASE, MEDLINE, and the Cochrane Library database, limited to English. Two authors (R.P., Y.A.) reviewed all identified abstracts and selected articles for full-text review. We included all articles that were reviews, meta-analyses, and original studies (cohort study, experimental study) assessing protein or inflammatory mediators about intra-abdominal sepsis. Articles that were letters, conference abstracts (no full-text available), and written articles about pediatric patients were excluded. Keywords for searching included abdominal sepsis, biomarkers, and inflammatory mediators.

Biomarkers

The metabolic, hemodynamic, and immune changes seen in sepsis occur through cytokines

and mediators that play a role in intercellular signal transmission.^{4,21} These biomarkers include measurement of acute-phase proteins, endothelial cell markers, chemokines, cytokines, leukocyte surface markers, damage-associated molecular patterns (DAMPs), non-coding ribonucleic acids (RNAs), micro RNA, and soluble receptors, as well as metabolites and alterations in gene expression (transcriptomics).²²

Biomarkers are measurable indicators used to define whether the disease state is normal or pathogenic. Biomarkers are markers that can be used to diagnose and treat disease, especially surgical diseases such as acute abdomen, cancer, etc. One of the most used methods in diagnosing and following many diseases is biomarkers.²³⁻²⁵ These markers can be used alone or with other auxiliary methods. Biomarkers play a critical role in the diagnosis of the disease, early recognition of organ dysfunction, disease risk classification, prognosis, and patient management.²²

Many markers have been identified as early markers of post-surgical infectious complications. In this study, especially the most commonly used markers with high diagnostic efficiency were discussed. It has been mentioned in some recent and experimental studies on new markers.

History of Mediators

C-reactive protein (CRP) is the oldest and most widely used mediator. Later, interleukins (IL-6, -8, and -10) and tumor necrosis factor- α (TNF- α) were reported as the most used markers. After 2000, procalcitonin (PCT) became a new marker in studies. More recently, endothelial dysfunction molecules and DAMPs have been added to the ever-growing list of inflammatory mediators.¹⁹

In clinical practice, white blood cell (WBC) count, CRP, and PCT are the most used parameters in the definition of abdominal infection.^{11,26,27}

Role of White Cell Count in the Diagnosis of Sepsis

White blood cell is one of the most widely used and easy-to-work hematological markers, especially in the diagnosis of inflammatory diseases. It is a marker with high diagnostic efficiency, especially in surgical conditions such as acute appendicitis.^{28,29} The diagnostic value of WBC in sepsis is limited. However, the criteria in the initial SIRS definition included an increase or decrease in the WBC count ($>12\,000$ or $<4000/\text{mm}^3$) or a normal WBC count with $>10\%$ bands. White blood cell levels can be raised in inflammation with non-infectious causes, making it rarely helpful as a sole diagnostic marker.^{5,30} However,

Main Points

- Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection according to sepsis-3 definitions.
- One of the essential sources of sepsis is abdominal infections.
- Intra-abdominal sepsis has high morbidity and mortality due to multiple and polymicrobial infection sources.
- In clinical practice, white blood cell count, C-reactive protein (CRP), and procalcitonin (PCT) are the most used parameters in the definition of abdominal infection.
- Persistent elevation of CRP or PCT levels in blood appears to be correlated with septic complications.

one of the WBC components, neutrophil, may be more valuable for sepsis. Neutrophil count increases during inflammation and relatively leads to lymphopenia. Thus, the neutrophil-to-lymphocyte ratio (NLR) increases. Neutrophil-to-lymphocyte has been used for the early prediction of inflammation in cases of mesenteric ischemia, acute appendicitis, and incarcerated hernia.^{24,31,32} Again, in intra-abdominal sepsis studies, the NLR value was associated with sepsis and its severity and was shown to be more significant than the WBC value.^{33,34}

C-Reactive Protein

The CRP and PCT are the most used markers to diagnose or exclude the diagnosis of IAI and have high diagnostic efficiency.^{13,35} Postoperative serum CRP and PCT levels increase on the first postoperative days 2 and 3. It reaches the peak level in the day and goes down to the normal level on the post-op seventh day. Postoperative increasing CRP levels after the fifth day suggest septic complications, such as anastomotic leakage or abscess.¹⁹

Procalcitonin

Procalcitonin is primarily secreted by the parafollicular C-cells of the thyroid gland and is the precursor of calcitonin. In the case of bacterial infection, cytokines, lipopolysaccharides (LPS), neutrophils, and brain, intestine, lung, and liver cells stimulate PCT production.³⁶ The PCT level is increased in bacterial and fungal infections but not in viral and non-infectious inflammation conditions. Procalcitonin is used in the diagnosis of IAIs and to guide antibiotic therapy.¹³ In the diagnosis of postoperative sepsis, ever-increasing PCT levels provide more valuable information in the diagnosis of postoperative sepsis than other markers. A PCT level of >1.1 ng/mL on the postoperative first day after major surgery is a precursor to complications such as anastomotic leakage or pneumonia, or sepsis to occur.³⁷

Interleukin-6

Interleukin-6 is one of the most used inflammatory indicators to evaluate infectious comorbidities. It is released in the early phases of inflammation. Interleukin-6 can also regulate hematopoietic function, immune response, and acute-phase response. Since it increases in correlation with the severity and duration of the infection, this marker is a valuable marker for predicting the prognosis and outcome of patients with sepsis.³⁸ In a recent study, Song et al³⁸ found that serum expression of TNF- α and IL-6 were associated with IAIs in patients after surgery. A composite of IL-6, PCT, and TNF- α can also increase the reliability of the

prediction of postoperative infections. In coronavirus disease-2019 patients, which is also a current disease, IL-6 is an early prognostic inflammatory mediator that determines the severity of the disease and IL-6 inhibitors can be used in the treatment of the disease.^{39,40}

Tumor Necrosis Factor-Alpha

Tumor necrosis factor- α is the major pro-inflammatory cytokine that plays a vital role in the anti-inflammatory and antimicrobial response by activating apoptosis of lymphocytes, cell proliferation, differentiation, and leukocytes.⁴¹ It is the earliest released and the most potent pro-inflammatory cytokine. Its release is stimulated in cases of injury and bacterial infection. Tumor necrosis factor- α peaks 6 hours after induction of sepsis and significantly increases in septic shock, correlated with the severity of the disease. Tumor necrosis factor- α ≥ 39.4 can be used as a predictor of sepsis risk.^{20,41} High concentrations of TNF- α can be used to predict septic infection risk. It plays a central role in TNF- α systemic inflammatory response. It directly affects septic shock, and the levels of this marker are associated with sepsis-induced death.⁴¹

Serum assays of several other markers, such as soluble CD14 subtypes (presepsin), proadrenomedullin, cytokines, DAMPs, or endothelial dysfunction molecules, have been proposed but are not commercially available for routine follow-up. Extensive cohort studies of these mediators are needed in the diagnosis of IAI.¹⁹

Damage-Associated Molecular Patterns

Tissue damage and shock lead to an extracellular release of associated molecular patterns (DAMPs). This leads to SIRS and hypoxia, reducing the resistance to infection and increasing the risk of sepsis.⁴² The best-known DAMPs is high-mobility group B1 (HMGB1). High-mobility group B1 is a deoxyribonucleic transcription factor that acts as a pro-inflammatory cytokine secreted from innate immune cells such as neutrophils, monocytes, and macrophages. In acute appendicitis studies, it gave more significant results than the WBC level.⁴³ There is a positive correlation between the severity and morbidity of the disease and the HMGB1 level in surgical patients. In another study, HMGB1 level was found to be higher in peritonitis than in control patients.⁴⁴ Compared with TNF- α and IL-1, it increases in the late phases of sepsis.⁴ Albayrak et al⁴⁵ found that inhibiting HMGB1 may reduce inflammation, fibrosis, and apoptosis and stop the progression of chronic liver disease.

Presepsin (Soluble CD14 Subtype)

In the last 10 years, many studies have been conducted on the effect of presepsin on sepsis, and it has been shown as a marker with high diagnostic value. Presepsin is a LPS-binding protein (LPS-LBP) complex receptor and is thought to be a fragment of CD14. Presepsin (soluble CD14 subtype) is generated in the bacterial infection condition and is expressed explicitly in sepsis.²⁶ Presepsin (soluble CD14 subtype) has the highest diagnostic accuracy for sepsis. Increased serum presepsin level correlates with PCT levels and reflects poor outcomes in patients with sepsis.^{26,46} In a recent study, the diagnostic efficiency of presepsin was higher than CRP and PCT in confirming the definition of abdominal sepsis.⁴⁷

Intraperitoneal Mediators

In patients with peritonitis, the peritoneal level of inflammatory mediators is 10-1000 times higher than the blood level. Measurement of peritoneal cytokine may be more valuable for assessing and monitoring the patient's reaction to inflammation.¹⁹

Other Less-Used Current Markers and New Therapeutic Agents or Novel Drug Targets

Some markers have not been applied in routine clinical practice but have recently been studied for their effectiveness. They can be used in the future diagnosis and follow-up of intra-abdominal sepsis. Markers, such as neutrophil CD64,¹¹ pancreatic stone protein,⁴⁸ 5-hydroxyindole acetic acid,⁴⁹ and Trefoil factor 3,⁵⁰ will better demonstrate their value in future studies. Since sepsis's pathogenesis is complex and accepted as a systemic disease, it is difficult to treat, and a standard treatment modality has not been determined yet.

Conclusions

Intra-abdominal infection is one of the leading causes of sepsis. The treatment process is complicated, and mortality is high. Although serum PCT and CRP are the most valuable markers in the diagnosis and treatment process of the disease, an ideal marker has not been determined yet. The issue of sepsis will continue to be up-to-date due to its economic consequences and the fact that it is still a disease with a very high mortality rate. Randomized controlled studies on this subject with large patient groups are needed to identify the ideal biomarkers and explain the roles of mediators in intra-abdominal sepsis. However, finding ideal markers will be difficult due to the complexity of sepsis and pathophysiological mechanisms.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – R.P., Y.A., E.A.; Design – R.P., F.Ş., S.S.A.; Supervision – R.P., E.A., S.S.A.; Funding – F.Ş., Y.A., S.S.A.; Materials – R.P., E.A., F.Ş., S.S.A.; Data Collection and/or Processing – R.P., F.Ş., Y.A., S.S.A.; Analysis and/or Interpretation – E.A., F.Ş., Y.A., S.S.A.; Literature Review – R.P., F.Ş., Y.A.; Writing Manuscript – R.P., Y.A., S.S.A.; Critical Review – R.P., F.Ş., S.S.A.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The authors declared that this study has received no financial support.

References

- Hecker A, Reichert M, Reuß CJ, et al. Intra-abdominal sepsis: new definitions and current clinical standards. *Langenbecks Arch Surg.* 2019;404(3):257-271. [\[CrossRef\]](#)
- Sartelli M, Catena F, Ansaloni L, et al. Complicated intra-abdominal infections in Europe: a comprehensive review of the CIAO study. *World J Emerg Surg.* 2012;7(1):36. [\[CrossRef\]](#)
- Boldingh QJ, de Vries FE, Boermeester MA. Abdominal sepsis. *Curr Opin Crit Care.* 2017;23(2):159-166. [\[CrossRef\]](#)
- Polat G, Ugan RA, Cadirci E, Halici Z. Sepsis and septic shock: current treatment strategies and new approaches. *Eurasian J Med.* 2017;49(1):53-58. [\[CrossRef\]](#)
- Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest.* 1992;101(6):1644-1655. [\[CrossRef\]](#)
- Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA.* 2016;315(8):801-810. [\[CrossRef\]](#)
- Kilinc Tokar A, Kose S, Turken M. Comparison of SOFA score, SIRS, qSOFA, and qSOFA+L criteria in the diagnosis and prognosis of sepsis. *Eurasian J Med.* 2021;53(1):40-47. [\[CrossRef\]](#)
- Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med.* 2013;369(9):840-851. [\[CrossRef\]](#)
- Ozturk G, Aydinli B, Atamanalp SS, Yildiran MI, Ozoğlu B, Kısaoğlu A. Acute mesenteric ischemia in young adults. *Wien Med Wochenschr.* 2012;162(15-16):349-353. [\[CrossRef\]](#)
- Hecker A, Uhle F, Schwandner T, Padberg W, Weigand MA. Diagnostics, therapy and outcome prediction in abdominal sepsis: current standards and future perspectives. *Langenbecks Arch Surg.* 2014;399(1):11-22. [\[CrossRef\]](#)
- Dimitrov E, Enchev E, Halacheva K, Minkov G, Yovtchev Y. Neutrophil CD64 - a potential biomarker in patients with complicated intra-abdominal infections? - a literature review. *Acta Microbiol Immunol Hung.* 2018;65(3):245-254. [\[CrossRef\]](#)
- Kryvoruchko IA, Sykal NA, Yevtushenko OV, Riabtev RS. A focus on abdominal sepsis: the problem of prognostic markers. *Med Sci.* 2021;25(114):2068-2076.
- Sartelli M, Coccolini F, Kluger Y, et al. WSES/GAIS/SIS-E/WSIS/AAST global clinical pathways for patients with intra-abdominal infections. *World J Emerg Surg.* 2021;16(1):49. [\[CrossRef\]](#)
- Ho J, Chan H, Liang Y, et al. Cathelicidin preserves intestinal barrier function in polymicrobial sepsis. *Crit Care.* 2020;24(1):47. [\[CrossRef\]](#)
- Assimakopoulos SF, Papadopoulou I, Bantouna D, et al. Fecal microbiota transplantation and hydrocortisone ameliorate intestinal barrier dysfunction and improve survival in a rat model of cecal ligation and puncture-induced sepsis. *Shock.* 2021;55(5):666-675. [\[CrossRef\]](#)
- Patoli D, Mignotte F, Deckert V, et al. Inhibition of mitophagy drives macrophage activation and antibacterial defense during sepsis. *J Clin Invest.* 2020;130(11):5858-5874. [\[CrossRef\]](#)
- Jin S, Jiang R, Lei S, et al. Shenfu injection prolongs survival and protects the intestinal mucosa in rats with sepsis by modulating immune response. *Turk J Gastroenterol.* 2019;30(4):364-371. [\[CrossRef\]](#)
- Gai X, Wang H, Li Y, et al. Fecal microbiota transplantation protects the intestinal mucosal barrier by reconstructing the gut microbiota in a murine model of sepsis. *Front Cell Infect Microbiol.* 2021;11:736204. [\[CrossRef\]](#)
- Xiao Z, Wilson C, Robertson HL, et al. Inflammatory mediators in intra-abdominal sepsis or injury - a scoping review. *Crit Care.* 2015;19:373. [\[CrossRef\]](#)
- Rutai A, Zsikai B, Tallósy SP, et al. A porcine sepsis model with numerical scoring for early prediction of severity. *Front Med (Lausanne).* 2022;9:867796. [\[CrossRef\]](#)
- Cheng B, Hoefl AH, Book M, Shu Q, Pastores SM. Sepsis: pathogenesis, biomarkers, and treatment. *BioMed Res Int.* 2015;2015:846935. [\[CrossRef\]](#)
- Barichello T, Generoso JS, Singer M, Dal-Pizzol F. Biomarkers for sepsis: more than just fever and leukocytosis - a narrative review. *Crit Care.* 2022;26(1):14. [\[CrossRef\]](#)
- Peksöz R, Albayrak Y, Şebil E, Dişçi E, Aşkin S, Yildiran Mİ. İ. Akut apandisit Hastalarında ghrelin Hormon Düzeyi Bakılması ve ghrelin Hormon Düzeyinin C-Reaktif protein ve beyaz kan hücre Düzeyleri ile Karşılaştırılması. *Genel Tıp Derg.* 2021;31(3):252-256. [\[CrossRef\]](#)
- Peksöz R, Karaislı S, Erözkan K, Ağırman E. The role of basic blood parameters in determining the viability of intestinal tissue in incarcerated hernias. *Int J Clin Pract.* 2021;75(10):e14664. [\[CrossRef\]](#)
- Uygur FA, Dişçi E, Peksöz R, Öztürk N, Yildiran Mİ, Albayrak Y. Diagnostic value of serum levels of galanin and obestatin in patients with gastric cancer. *Rev Assoc Med Bras (1992).* 2022;68(7):888-892. [\[CrossRef\]](#)
- Vodnik T, Kaljevic G, Tadic T, Majkic-Singh N. Presepsin (sCD14-ST) in preoperative diagnosis of abdominal sepsis. *Clin Chem Lab Med.* 2013;51(10):2053-2062. [\[CrossRef\]](#)
- Jung B, Molinari N, Nasri M, et al. Procalcitonin biomarker kinetics fails to predict treatment response in perioperative abdominal infection with septic shock. *Crit Care.* 2013;17(5):R255. [\[CrossRef\]](#)
- Rimmer E, Garland A, Kumar A, et al. White blood cell count trajectory and mortality in septic shock: a historical cohort study [Évolution de la numération leucocytaire et mortalité en cas de choc septique: une étude de cohorte historique]. *Can J Anaesth.* 2022;69(10):1230-1239. [\[CrossRef\]](#)
- Peksöz R, Dişçi E, Kaya A, et al. Significance of laboratory parameters in diagnosing acute appendicitis during pregnancy. *ANZ J Surg.* 2022;92(1-2):121-127. [\[CrossRef\]](#)
- Farkas JD. The complete blood count to diagnose septic shock. *J Thorac Dis.* 2020;12(suppl 1):S16-S21. [\[CrossRef\]](#)
- Yeni M, Peksöz R. The role of basic laboratory parameters in diagnosing acute appendicitis and determining disease severity in the elderly. *Turk J Colorectal Dis.* 2022;32(2):110-116. [\[CrossRef\]](#)
- Karadeniz E, Bayramoğlu A, Atamanalp SS. Sensitivity and specificity of the platelet-lymphocyte ratio and the neutrophil-lymphocyte ratio in diagnosing acute mesenteric ischemia in patients operated on for the diagnosis of mesenteric ischemia: a retrospective case-control study. *J Invest Surg.* 2020;33(8):774-781. [\[CrossRef\]](#)
- Liu S, Li Y, She F, Zhao X, Yao Y. Predictive value of immune cell counts and neutrophil-to-lymphocyte ratio for 28-day mortality in patients with sepsis caused by intra-abdominal infection. *Burns Trauma.* 2021;9:tkaa040. [\[CrossRef\]](#)
- Mousa N, Besheer T, Abdel-Razik A, et al. Can combined blood neutrophil to lymphocyte ratio and C-reactive protein be used for diagnosis of spontaneous bacterial peritonitis? *Br J Biomed Sci.* 2018;75(2):71-75. [\[CrossRef\]](#)
- Montravers P, Tashk P, Tran Dinh A. Unmet needs in the management of intra-abdominal infections. *Expert Rev Anti Infect Ther.* 2017;15(9):839-850. [\[CrossRef\]](#)
- Sridharan P, Chamberlain RS. The efficacy of procalcitonin as a biomarker in the management of sepsis: slaying dragons or tilting at windmills? *Surg Infect (Larchmt).* 2013;14(6):489-511. [\[CrossRef\]](#)
- Mokart D, Merlin M, Sannini A, et al. Procalcitonin, interleukin 6 and systemic inflammatory response syndrome (SIRS): early markers of postoperative sepsis after major surgery. *Br J Anaesth.* 2005;94(6):767-773. [\[CrossRef\]](#)
- Song J, Lu Y. Composite inflammatory indicators as early predictor of intra-abdominal infections after general surgery. *J Inflamm Res.* 2021;14:7173-7179. [\[CrossRef\]](#)
- Kesmez Can F, Özkurt Z, Öztürk N, Sezen S. Effect of IL-6, IL-8/CXCL8, IP-10/CXCL10 levels on the severity in COVID 19 infection. *Int J Clin Pract.* 2021;75(12):e14970. [\[CrossRef\]](#)

40. Coomes EA, Hagbayan H. Interleukin-6 in Covid-19: a systematic review and meta-analysis. *Rev Med Virol.* 2020;30(6):1-9. [\[CrossRef\]](#)
41. Zhai GH, Zhang W, Xiang Z, et al. Diagnostic value of sIL-2R, TNF- α and PCT for sepsis infection in patients with closed abdominal injury complicated with severe multiple abdominal injuries. *Front Immunol.* 2021;12:741268. [\[CrossRef\]](#)
42. Zhang Q, Raoof M, Chen Y, et al. Circulating mitochondrial DAMPs cause inflammatory responses to injury. *Nature.* 2010;464(7285):104-107. [\[CrossRef\]](#)
43. Albayrak Y, Albayrak A, Celik M, et al. High mobility group box protein-1 (HMGB-1) as a new diagnostic marker in patients with acute appendicitis. *Scand J Trauma Resusc Emerg Med.* 2011;19:27. [\[CrossRef\]](#)
44. Wu C, Sun H, Wang H, et al. Evaluation of high mobility group box 1 protein as a presurgical diagnostic marker reflecting the severity of acute appendicitis. *Scand J Trauma Resusc Emerg Med.* 2012;20:61. [\[CrossRef\]](#)
45. Albayrak A, Uyanik MH, Cerrah S, et al. Is HMGB1 a new indirect marker for revealing fibrosis in chronic hepatitis and a new therapeutic target in treatment? *Viral Immunol.* 2010;23(6):633-638. [\[CrossRef\]](#)
46. Shirakawa K, Naitou K, Hirose J, Takahashi T, Furusako S. Presepsin (sCD14-ST): development and evaluation of one-step ELISA with a new standard that is similar to the form of presepsin in septic patients. *Clin Chem Lab Med.* 2011;49(5):937-939. [\[CrossRef\]](#)
47. Juroš GF, Tomičić M, Šarić SD, Perić M, Rogić D. Contribution of presepsin, procalcitonin and C-reactive protein to the SOFA score in early sepsis diagnosis in emergency abdominal surgical patients. *Signa Vitae.* 2019;15(1):38-45. [\[CrossRef\]](#)
48. Ventura F, Gasche Y, Rached AKB, et al. Pancreatic stone protein as a biomarker for the early diagnosis of post-operative peritonitis, intra-abdominal infection and sepsis. *J Surg Case Rep.* 2022;2022(11):rjac497. [\[CrossRef\]](#)
49. Li F, Jiang L, Pan S, et al. Multi-omic profiling reveals that intra-abdominal-hypertension-induced intestinal damage can be prevented by microbiome and metabolic modulations with 5-hydroxyindoleacetic acid as a diagnostic marker. *mSystems.* 2022;7(3):e0120421. [\[CrossRef\]](#)
50. Meijer MT, Uhel F, Cremer OL, et al. Elevated trefoil factor 3 plasma levels in critically ill patients with abdominal sepsis or non-infectious abdominal illness. *Cytokine.* 2020;133:155181. [\[CrossRef\]](#)