

# **EARLY RECOGNITION OF SEPSIS: AN INTEGRATIVE REVIEW OF THE LITERATURE ON CLINICAL SYMPTOMS AND FUTURE PERSPECTIVES**

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**Abstract: Goal:** Gather the most recent work and studies on the early recognition of sepsis. **Methodology:** Integrative literature review in the United States National Library of Medicine (PubMed), Sciverse Scopus (Scopus) and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). Following the following inclusion criteria: articles in full version available free of charge, published in the last 5 years, in Portuguese, Spanish and English, with free access on ``Universidade Federal do Rio de Janeiro`` (UFRJ) network, studies carried out among adults and studies that address the early signs and symptoms of sepsis and the exclusion criteria were: articles that address the treatment, management, outcome and consequences of sepsis, articles focused on specific clinics, basic research articles, case studies, bundles, editorials, letters to the editor, clinical protocols and conference papers. **Results and Discussion:** A total of 267 articles were found, of which, after analyzing the title and abstract, 34 were selected to compose this review. **Conclusion:** There is still great difficulty in obtaining an early diagnosis of sepsis. Studies have been carried out in search of new biochemical markers that can indicate and determine the diagnosis of sepsis and its possible complications. Limitations are noted in the present diagnostic methods, and it is recommended that they be used together and not individually.

**Keywords:** Early sepsis recognition

## INTRODUCTION

According to the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM – 2016), sepsis is defined as “the presence of life-threatening organic dysfunction secondary to the host’s dysregulated response to an infection”. It is an exacerbated systemic reaction triggered by the presence of inflammatory chemical mediators produced in response to a

host agent or toxin produced by it in a specific location in the body and which then reach the bloodstream, affecting the entire organism. It is considered an acute condition, which can quickly evolve into septic shock - being more difficult to reverse - and consequently systemic dysfunction. According to the Latin American Sepsis Institute (ILAS – 2016), sepsis is among the biggest causes of death in hospitalized patients in the world. The aging of the population and the increase in the number of immunosuppressed people or people with chronic diseases have contributed to the impact of sepsis on the world population. Added to this is the growing resistance of microorganisms against the antibiotics currently available in the clinic, a condition that represents a complicating element for the treatment and reversal of sepsis. “Estimates indicate the existence of approximately 600 thousand new cases of sepsis each year in Brazil. This scenario has a direct impact on morbidity and mortality indicators, with the consequences of sepsis being responsible for the causes of 16.5% of death certificates issued, that is, around 250 thousand cases. This is a serious challenge for public health.” (ILAS, 2018). In this context, early recognition is extremely important so that there is a good prognosis for the patient. The Nursing team plays a fundamental role in the early identification of sepsis, as it is the professional category that is “at the bedside” at all times during hospital admission, having more opportunities to identify sepsis early, and must therefore be attentive which may indicate initial signs and symptoms of this syndrome.

## METHODOLOGY

This is an exploratory study, according to the bibliographic research method in an integrative literature review, based on the guiding question “What are the main early

signs and symptoms of sepsis described in the literature?”. The PICo strategy was used to search the databases, representing “P” the population, which in this case are adults, “I”, the interest, which are the early signs of sepsis and “Co”, the context, which is sepsis. The objective of this study is to bring together the most recent works and studies on the subject presented.

The search was carried out on January 11, 2022, using the United States National Library of Medicine (PubMed), Sciverse Scopus (Scopus) and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) as databases. The Health Sciences Descriptors (DeCS) “early sepsis recognition” were adopted. As inclusion criteria, articles were considered in full version available free of charge, published in the last 5 years, in Portuguese, Spanish and English, with free access on the network of “Universidade Federal do Rio de Janeiro” (UFRJ), studies carried out among adults and studies that address the early signs and symptoms of sepsis. Exclusion criteria included articles that address the treatment, management, outcome and consequences of sepsis, articles focused on specific clinics, basic research articles, case studies, bundles, editorials, letters to the editor, clinical protocols and conference papers. To select the articles, all titles were read and those that were related to the study question were selected. The abstracts were then analyzed and those that were related to the topic at hand were selected for full reading. To categorize the data, an instrument was created with data relating to the identification of the article (article title, authors, journal of publication, year of publication, periodical, design, type of study, objective, main results and conclusions).

## RESULTS

From the selected descriptors, 80 articles

were found in the scientific database of the United States National Library of Medicine (PubMed), 145 articles in the Sciverse Scopus database (Scopus) and 42 articles in the Cumulative Index to Nursing and Allied database Health Literature (CINAHL). After applying the exclusion criteria and filters described in the methodology, 34 articles were analyzed to write this integrative literature review (figure 1).

The main data from these articles are detailed in the two tables below.

## DISCUSSION

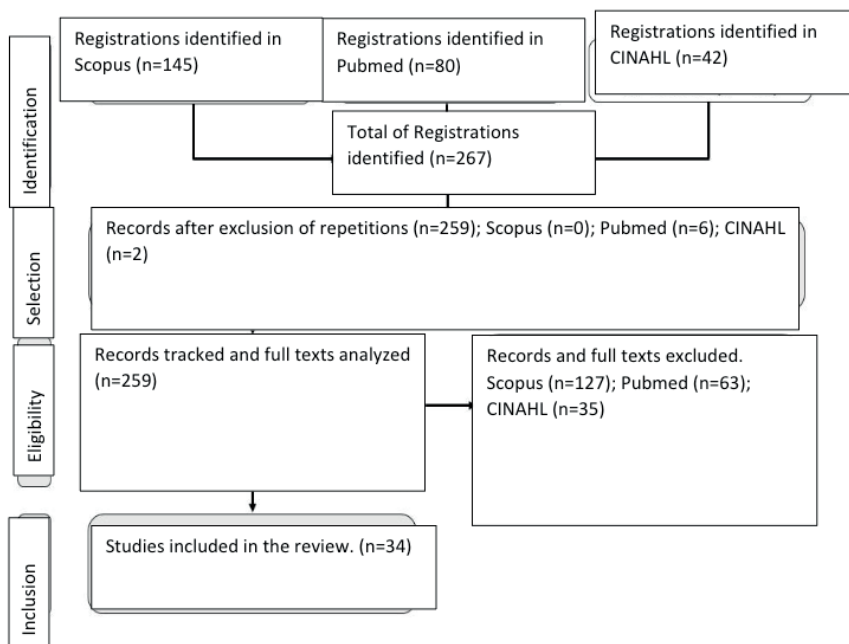
### EARLY SIGNS

According to ILAS (2018), the main organic dysfunctions present in sepsis can be assessed using the Sequential Organ Failure Assessment (SOFA) and quick SOFA scores. The signs evaluated by these scores include: Hypotension (SBP < 90 mmHg or MAP < 65 mmHg or drop in BP > 40 mmHg), oliguria ( $\leq 0.5\text{mL/Kg/h}$ ) or increase in creatinine ( $>2\text{mg/dL}$ ), relationship PaO<sub>2</sub>/FiO<sub>2</sub> < 300 or need for O<sub>2</sub> to maintain SpO<sub>2</sub> > 90%, platelet count < 100,000/mm<sup>3</sup> or 50% reduction in the number of platelets in relation to the highest value recorded in the last three days, lactate above the reference value, decreased level of consciousness, agitation, delirium, significant increase in bilirubin ( $>2\text{X}$  the reference value) (ILAS, 2018). Also according to ILAS 2018, sepsis that progresses to hypotension not corrected with volume replacement (MAP  $\leq 65$  mmHg) is defined as septic shock” (ILAS, 2018, p.4). Studies 2, 3 and 22, obtained in the bibliographic search of this research, reinforce the importance given by ILAS to such signs as early predictors of organic dysfunctions presented in this syndrome.

Some authors, such as Prasad, Priya A et al (2020); Polilli, Ennio et al (2020); Amland, Robert C, and Kristin E Hahn-Cover (2019); Kim, Hwan Il, and Sunghoon Park (2019)

Database	Search strategy
PubMed	("early"[All Fields] AND ("sepsis"[MeSH Terms] OR "sepsis"[All Fields]) AND ("recognition, psychology"[MeSH Terms] OR ("recognition"[All Fields] AND "psychology"[All Fields]) OR "psychology recognition"[All Fields] OR "recognition"[All Fields] OR "recognitions"[All Fields])) AND ((y_5[Filter]) AND (ffrt [Filter]) AND (English [Filter] OR portuguese[Filter] OR Spanish Filter)) AND (alladult[ Filter]))
Scopus	TITLE-ABS-KEY ( early AND sepsis AND recognition AND adults) AND ( LIMIT-TO ( OA, "all") AND ( LIMIT-TO ( PUBYEAR, 2022) OR LIMIT-TO ( PUBYEAR, 2021) OR LIMIT-TO ( PUBYEAR, 2020) OR LIMIT-TO ( PUBYEAR, 2019) OR LIMIT-TO ( PUBYEAR, 2018) OR LIMIT-TO ( PUBYEAR, 2017) AND ( LIMIT-TO ( LANGUAGE, "English") OR LIMIT-TO ( LANGUAGE, "Spanish")
CINAHL	early sepsis recognition (Limiters - Full text; Publication date: 20170101-20221231 Expanders - Apply equivalent subjects Search modes - Boolean/Phrase)

**Table 1:** Search strategies in databases for analyzing records



**Figure 1**

<b>Id.</b>	<b>Title</b>	<b>Authors</b>	<b>Year</b>	<b>Place</b>	<b>Newspaper</b>
1	<i>Diagnostic and prognostic capabilities of a biomarker and EMR-based machine learning algorithm for sepsis.</i>	Taneja, Ishan <i>et al.</i>	2021	United States	Clinical and Translational Science
2	<i>Telephonic description of sepsis among callers to an emergency dispatch centre in South Africa</i>	Stassen, Willem <i>et al</i>	2020	South Africa	African Journal of Emergency Medicine
3	<i>Update of Sepsis in the Intensive Care Unit</i>	Genga, Kelly e Russel, James	2017	Canad	Journal of Innate Immunity
4	<i>Diagnostic accuracy of procalcitonin, neutrophil-lymphocyte count ratio, C-reactive protein, and lactate in patients with suspected bacterial sepsis.</i>	Ljungström, Lars <i>et al</i>	2017	Sweden	Plos One
5	<i>Recognition of sepsis in primary care: a survey among GPs.</i>	Loots, Feike J <i>et al</i>	2017	Norway	BJGP Open
6	<i>Serial measurement of pancreatic stone protein for the early detection of sepsis in intensive care unit patients: a prospective multicentric study.</i>	Pugin, Jérôme <i>et al</i>	2021	RU, France, Switzerland and Italy	Critical Care
7	<i>Early Prediction of Sepsis in the ICU Using Machine Learning: A Systematic Review.</i>	Moor, Michael <i>et al</i>	2021	Switzerland	Frontiers in Medicine
8	<i>Role of international normalized ratio in nonpulmonary sepsis screening: An observational study.</i>	Zhang, Jing <i>et al</i>	2021	China	World Journal of Clinical Cases
9	<i>Artificial Intelligence Pulse Coupled Neural Network Algorithm in the Diagnosis and Treatment of Severe Sepsis Complicated with Acute Kidney Injury under Ultrasound Image.</i>	Ying, Fu <i>et al</i>	2021	China	Journal of Healthcare Engineering
10	<i>Cutting-Edge Technology for Rapid Bedside Assessment of Capillary Refill Time for Early Diagnosis and Resuscitation of Sepsis.</i>	Sheridan, David C <i>et al</i>	2020	United States	Frontiers in Medicine
11	<i>Comparison of Monocyte Distribution Width (MDW) and Procalcitonin for early recognition of sepsis.</i>	Polilli, Ennio <i>et al</i>	2020	Italy	Plos one
12	<i>Clinical Decision Support for Early Recognition of Sepsis.</i>	Amland, Robert C, e Kristin E Hahn-Cover	2019	United States	American Journal of Medical Quality
13	<i>Robustness of sepsis-3 criteria in critically ill patients</i>	Verboom, Diana M <i>et al</i>	2019	Netherlands	Journal of intensive care
14	<i>Monocyte Distribution Width: A Novel Indicator of Sepsis-2 and Sepsis-3 in High-Risk Emergency Department Patients</i>	Crouser, Elliott D <i>et al</i>	2019	United States	Critical Care Medicine
15	<i>Presepsin level in predicting patients' in-hospital mortality from sepsis under sepsis-3 criteria.</i>	Wen, Miao-Yun <i>et al</i>	2019	China	Therapeutics and Clinical Risk Management
16	<i>Sepsis: Early Recognition and Optimized Treatment</i>	Kim, Hwan Il, e Sunghoon Park	2019	Korea	Tuberculosis and Respiratory Diseases
17	<i>Early Sepsis Detection in Critical Care Patients Using Multiscale Blood Pressure and Heart rate Dynamics</i>	Shashikumar, Supreeth P <i>et al</i>	2017	United States	Journal of Electrocardiology

18	<i>Screening for sepsis in general hospitalized patients: a systematic review</i>	Alberto, Laura <i>et al</i>	2017	Australia	Journal of Hospital Infection
19	<i>An Interpretable Machine Learning Model for Accurate Prediction of Sepsis in the ICU</i>	Nemati, Shamim <i>et al</i>	2018	United States	Critical Care Medicine
20	<i>Clinical and microbiological characterization of sepsis and evaluation of sepsis scores.</i>	Fuchs, Andre <i>et al</i>	2021	Germany, Spain and Ethiopia	Plos One
21	<i>The Early Recognition and Management of Sepsis in Sub-Saharan African Adults: A Systematic Review and Meta-Analysis</i>	Morton, Ben <i>et al</i>	2018	Kenya	International Journal of Environmental Research and Public Health
22	<i>Early diagnosis of sepsis in emergency departments, time to treatment, and association with mortality: An observational study.</i>	Husabø, Gunnar <i>et al</i>	2020	Norway	Plos One
23	<i>Sepsis recognition tools in acute ambulatory care: associations with process of care and clinical outcomes in a service evaluation of an Emergency Multidisciplinary Unit in Oxfordshire.</i>	Camm, Christian Fielder <i>et al</i>	2018	United Kingdom	BMJ open
24	<i>Circulating lymphocyte subsets as promising biomarkers to identify septic patients at higher risk of unfavorable outcome.</i>	Polilli, Ennio <i>et al</i>	2021	Italy	BMC Infectious
25	<i>Time to Recognition of Sepsis in the Emergency Department Using Electronic Health Record Data: A Comparative Analysis of SIRS, SOFA, and qSOFA.</i>	Prasad, Priya A <i>et al</i>	2020	United States	Critical Care Medicine
26	<i>Use of Biomarkers to Identify Acute Kidney Injury to Help Detect Sepsis in Patients With Infection.</i>	Kellum, John A <i>et al</i>	2021	Spain, USA, Belgium and France	Critical Care Medicine
27	<i>The shape change index (SCI) of inferior vena cava (IVC) measuring by transabdominal ultrasound to predict the presence of septic shock in intensive care unit (ICU) patients.</i>	<b>Huan, C</b> <i>et al</i>	2019	China	European Review for Medical and Pharmacological Sciences
28	<i>Diagnostic Accuracy of Procalcitonin and C-reactive Protein Is Insufficient to Predict Proven Infection: A Retrospective Cohort Study in Critically Ill Patients Fulfilling the Sepsis-3 Criteria.</i>	van Oers, J A H <i>et al</i>	2020	Netherlands	<i>The Journal of Applied Laboratory Medicine</i>
29	<i>Multiscale Network Representation of Physiological Time Series for Early Prediction of Sepsis.</i>	Shashikumar, Supreeth P <i>et al</i>	2017	United States	Physiological measurement
30	<i>Sepsis now a priority: a quality improvement initiative for early sepsis recognition and care.</i>	McDonald, Christine M <i>et al</i>	2018	Canada	International Journal for Quality in Health Care
31	<i>The prognostic utility of protein C as a biomarker for adult sepsis: a systematic review and meta-analysis</i>	Catenacci, V <i>et al</i>	2022	Canada	Critical Care

32	<i>Circulating lymphocyte subsets as promising biomarkers to identify septic patients at higher risk of unfavorable outcome.</i>	Polilli, Ennio <i>et al</i>	2021	Italy	BMC Infectious Diseases
33	<i>Machine learning for the prediction of sepsis: a systematic review and meta-analysis of diagnostic test accuracy.</i>	Fleuren, Lucas M <i>et al</i>	2020	Netherlands	Intensive Care Medicine
34	<i>Clinical Scores and Formal Triage for Screening of Sepsis and Adverse Outcomes on Arrival in an Emergency Department All-Comer Cohort.</i>	Nieves Ortega, Ricardo <i>et al</i>	2019	Suíça	The Journal of Emergency Medicine

**Table 1:** Distribution of studies according to Title, Authors, Year, Place and Periodical (Macaé, Rio de Janeiro, Brazil, 2022)

<b>Id.</b>	<b>Design</b>	<b>Goal</b>	<b>Main results</b>	<b>Conclusion</b>
1	Cohort study	Determine the diagnostic and prognostic capacity of machine learning algorithms based on clinical data and a set of biomarkers not commonly measured.	Risk prediction scores for patients with septic shock were higher compared to those without shock ( $p < 0.0001$ ). Scores for patients with infection or organ dysfunction were higher compared to those without any of these conditions ( $p < 0.0001$ ). Stratification based on the prediction scores of groups of patients with low, medium and high risk, showed significant differences in length of stay ( $p < 0.0001$ ), mortality within 30 days ( $p < 0.0001$ ), and readmission to hospital within 30 days ( $p < 0.0001$ ).	In conclusion, the machine learning algorithm based on the electronic medical record and the measurement of non-routine markers demonstrated good ability to diagnose and prognose at the time of the initial blood culture.
2	Retrospective observational study	Determine keywords used by users to describe patients with sepsis in South Africa when calling the national private emergency center.	Eleven distinct categories were identified. The main categories used to describe sepsis over the telephone were: gastrointestinal symptoms (40%), acute altered mental status (35%), leg weakness (33%), and malaise (31%). At least one of these four keyword categories appeared in 86% of all recorded calls.	It was found that certain categories appeared more frequently than others for a pattern to be recognized. Using these categories, telephone recognition algorithms for sepsis can be developed to help predict sepsis over the telephone. This would allow the attendant to immediately identify the level of care and could thus lead to positive effects on patient outcome.
3	Integrative Literature Review	Consider, summarize and discuss the main studies on sepsis in 2016.	Several randomized controlled trials that analyzed new (and old) interventions in sepsis/septic shock are discussed in this review in parallel with the SSC 2016 recommendations and other guidelines where relevant. Randomized controlled trials that address incidence, treatment, and prevention of important organ dysfunction associated with sepsis such as acute respiratory distress syndrome, acute kidney injury, and brain dysfunction are highlighted.	The need for new targets, predictive biomarkers and new RCT designs in sepsis is discussed.

4	Prospective observational study	To investigate the performance characteristics of sepsis biomarkers, alone and in combination, for diagnosing verified bacterial sepsis using the Sepsis 2 and Sepsis 3 criteria, respectively.	For the diagnosis of bacterial sepsis based on the Sepsis-3 criteria, the AUC for PCT (0.68; 95% CI 0.65–0.71) was comparable to the AUCs for the two composite biomarkers. Using the Sepsis-2 criteria for diagnosing bacterial sepsis, the AUC for the NLCR (0.68; 95% CI 0.65–0.71), but not for the other individual biomarkers, was equal to the AUCs for the two biomarkers. compounds. For the diagnosis of severe bacterial sepsis or septic shock based on the Sepsis-2 criteria, the AUCs for both composite biomarkers were significantly higher than those for the single biomarkers (0.85; 95% CI 0.82–0.88 for the composite biomarker of three and 0.86; 95% CI 0.83–0.89 for the composite biomarker of four).	The combination of biomarkers can improve the diagnosis of bacterial sepsis seen in the most severe patients, but in less severe sepsis conditions neither NLCR or PCT alone exhibit equivalent performance.
5	Quantitative study based on the Likert scale	Obtain clinical decision-making information from GPs (General practitioners) in patients with possible septic infection.	Based on self-reported cases of possible serious infections, the factors that were most indicated as important in the decision to take patients to the hospital were: general appearance (92.1%), history (92.0%), and physical examination (89.3%). Temperature (88.7%), heart rate (88.7%), and blood pressure (82.1%) were the most frequently measured vital signs. In general, GPs were likely to refer patients in case of: altered mental status (98.7%), systolic blood pressure <100mmHg (93.7%), inability to stand (89.3%), insufficient prior effect of antibiotic therapy (87.4%), and respiratory rate $\geq$ 22/minute (86.1%).	GPs' assessment of patients with possible serious infection is a complex process, in which in addition to checking vital signs, several other aspects of the consultation guide the decision to refer the patient to hospital. To improve the care of patients with sepsis, diagnosis and prognosis, which value the assessment of vital signs and symptoms, GPs' intuition, and additionally diagnostic tests, must be studied prospectively in the primary care context.
6	International multicenter prospective observational clinical study	To explore the potential of serial measurements of C-reactive protein, procalcitonin, and pancreatic stone protein for early recognition of sepsis in patients hospitalized in the intensive care unit.	The clinical diagnosis of sepsis was associated with increased biomarker values 3 days before diagnosis [PSP (p = 0.003), PCT (p = 0.025) and CRP (p = 0.009)]. Pancreatic stone protein began to increase 5 days before the clinical diagnosis of sepsis. Procalcitonin 3 and C-reactive protein 2 days, respectively. The area under the ROC curve at the time of clinical sepsis was similar for all markers (PSP, 0.75; CRP, 0.77; PCT, 0.75).	While the accuracy of PSP, PCT and PCR for sepsis was similar in this cohort, serum PSP demonstrated an increase in this marker in the days before the onset of signs necessary for the clinical diagnosis of sepsis. This observation warrants further evaluation of the beneficial potential of serum PSP measurement in the management of critically ill patients who develop nosocomial sepsis.



7	Systematic review	To systematically review and evaluate studies involving machine learning for the prediction of sepsis in the ICU.	The majority of studies (n=19, 86.4%) involved an offline training scenario combined with an assessment horizon, while two studies implemented an online scenario (n=2, 9.1%). The enormous heterogeneity between studies in terms of model development, definition of sepsis, prediction time windows, and outcomes precluded a meta-analysis. Lastly, only two studies provided publicly accessible source code and data sources, promoting reproducibility.	There has been a growing number of studies involving machine learning to optimize the early prediction of sepsis through the discovery of digital biomarkers. This review, however, highlights several shortcomings of current approaches, including poor comparability and reproducibility. Finally, recommendations were gathered on how these challenges can be addressed before implementing these models in prospective analyses.
8	Prospective observational study	To investigate the effectiveness of the International Normalized Ratio (INR) for the early and rapid recognition of non-pulmonary infectious sepsis in adults.	The INR values in the sepsis groups were significantly higher than in the non-septic groups. INR has a superior diagnostic efficacy for sepsis, with an area under the curve value of 0.918, when those pre-existing diseases that significantly affect coagulation function have been excluded. The diagnostic efficacy of INR was more significant than that of NLCR, PLT and qSOFA ( $P < 0.05$ ). Furthermore, INR levels of 1.17, 1.20, and 1.22 can be used to categorize the relative risk of nonpulmonary infection sepsis into three categories: low, medium, and high risk, respectively.	The INR is a promising and easy-to-obtain biomarker for diagnosis and can be used as one of the indicators for early screening of non-pulmonary infectious sepsis. When its value is higher than the ideal cutoff value (1.22), high surveillance for non-pulmonary infectious sepsis in adults is required.
9	Prospective observational study	The aim of this study was to explore the diagnosis of severe sepsis complicated with acute kidney injury (AKI) by ultrasonic image information based on artificial intelligence pulse-coupled neural network (PCNN) algorithm.	It was found that the histogram distribution of this algorithm was relatively uniform, and the information of each gray level was obviously retained and enhanced, which had the best effect on this algorithm; there was a marked individual difference in RRI values. Overall, RRI values showed a slight upward trend after intensive care unit (ICU) admission. The RRI was taken as the dependent variable, time as the fixed effect model and patients as the random effect; the value of the time parameter was between 0.012 and 0.015, $p = 0.000 < 0.05$ . Furthermore, there was no significant difference in the ultrasonic score between the different time measurements ( $t = 1.348$ and $p = 0.128 > 0.05$ ). The area under the RRI ROC curve for the diagnosis of AKI on the 2nd day, 4th day and 6th day was 0.758, 0.841 and 0.856, respectively, all greater than 0.5 ( $p < 0.05$ ).	The algorithm proposed in this study could significantly increase the amount of information in ultrasound images. Furthermore, change in IRR values measured by ultrasound images based on PCNN artificial intelligence was associated with AKI.

10	New Technology Assessment Study	Introduce new technology that was developed through a problem-based innovation approach to enable clinicians to quickly assess end organ perfusion at bedside triage or in the emergency department and be incorporated into the electronic medical record.	This new technology has 3 significant advantages: [1] the use of reflected light technology for capillary refill assessment to provide deeper tissue penetration with a lower signal-to-noise ratio than transmitted infrared light, [2] the ability to significantly improve clinical outcomes without major changes to clinical workflow or provider practice, and [3] can be used by individuals with minimal training and even in low-resource settings to increase the utility of this technology.	The current device is ready for clinical research and is being tested in both the ICU and emergency department to further validate its clinical evidence.
11	Prospective observational study	To evaluate whether monocyte distribution width (MDW) may play a role in identifying patients with sepsis compared to procalcitonin (PCT); n=260.	Sepsis was diagnosed in 105 (40.4%); in 60 (57.1%) at least 1 microorganism was isolated from blood cultures. The best statistical cutoffs associated with sepsis were 22.0 for MDW and 1.0 ng/mL for PCT, while MDW values <20 were invariably associated with negative blood cultures. In the ROC curve analysis, the AUC of MDW (0.87) was almost overlapped with that of PCT (0.88).	The observed data suggest that incorporation of MDW within current routine WBC counts and indices may be of notable use for sepsis detection.
12	Multicenter retrospective study	Determine the clinimetric performance of a computerized cloud-based sepsis clinical decision support system (CDS), understand the epidemiology of sepsis, and identify opportunities for quality improvement.	The data covered 6,200 adult hospitalizations from 2012 to 2013. Of the 13% of patients screened, 51% were already suspected of infection when the system was activated. This study focused on a cohort of patients screened before infection was suspected; the average time from arrival to activation of the CDS was 3.5 hours and activation of the system for diagnostic collection was another 8.6 hours.	The Sepsis CDS enables providers to accelerate diagnostic and therapeutic interventions and provides transparency into hospital-wide care management, with the goal of reversing a patient's sepsis syndrome to prevent serious complications such as organ system dysfunction and death. The system's measurement of accuracy can be improved by providers performing 2 or 3 different types of diagnostics (e.g., microbiology, serology, chemistry, lactic acid cultures).
13	Prospective cohort study	To evaluate the accuracy of sepsis-3 criteria in intensive care unit (ICU) patients.	Among 1,081 patients with suspected infection on ICU admission, 648 (60%) were considered to have sepsis according to prospective adjudication in the MARS study, while 976 (90%) met sepsis-3 criteria, resulting in only 64 % agreement at individual patient level. Compared with prospectively recorded MARS sepsis events, more patients met criteria for sepsis-3 and septic shock-3 on ICU admission (60% vs 90% and 27% vs 38%, respectively). Furthermore, agreement between definitions was only 64% and 80%, respectively. For patients with ICU-acquired infections, the overall incidences of sepsis (54% vs 52%) and septic shock (19% vs 18%) were similar, but the MARS and sepsis-3 criteria selected different individuals (58% and 81% concordance for sepsis and septic shock, respectively).	The definition of sepsis-3 lacks accuracy and discriminatory capacity, since almost all patients who arrive at the ICU with suspected infection meet its criteria. These must therefore be specified in more detail, and applied more consistently, during future sepsis studies.

14	Prospective observational study of cohort	To evaluate the diagnostic accuracy of peripheral blood monocyte distribution alone and in combination with leukocyte count for early detection of sepsis in the emergency department.	The negative predictive values for monocyte distribution less than or equal to 20 U for Sepsis-2 and Sepsis-3 were 93% and 94%, respectively. Monocyte distribution greater than 20.0 U combined with an abnormal WBC further improved detection of Sepsis-2 (area under the curve, 0.85; 95% CI, 0.83–0.88) and as reflected by likelihood ratio and value-added analyses. The normal distribution width of leukocytes and monocytes inferred a six-fold lower probability of sepsis.	A monocyte distribution width value greater than 20.0 U is effective for detecting sepsis, based on Sepsis-2 or Sepsis-3 criteria, during initial care in the emergency department. In conjunction with WBC, monocyte distribution width is further predicted to improve medical decision making during early treatment of sepsis in the emergency department.
15	Prospective observational study	To evaluate the effect of presepsin level in predicting the prognosis of patients with sepsis under the sepsis-3 criteria.	The presepsin level of the non-survivor group was significantly higher than that of the survivor group. Binary logistic regression showed that the pre-sepsin level was an independent risk factor for hospital mortality in patients due to sepsis.	Pre-sepsin is a prognostic biomarker with high accuracy in predicting the prognosis of sepsis under the sepsis-3 criteria.
16	Integrative literature review	Identify articles in the literature that address early recognition and optimized treatment of sepsis.	Three subsequent multicenter randomized controlled trials (RCTs) did not show that EGDT reduced the sepsis mortality rate compared with usual care. Recently, new definitions of sepsis were issued by the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) for screening and early identification.	Prevention and early recognition of sepsis are of paramount importance until new emerging medications (or interventions) are demonstrated to be effective. Early application of optimal treatments and better adherence to sepsis packages are prerequisites for improving patient outcomes.
17	Prospective observational study	To investigate the utility of high-resolution blood pressure (BP) and heart rate (HR) time series dynamics for early prediction of sepsis in patients at an urban teaching hospital, meeting the third international consensus definition of sepsis (sepsis-III) during his admission to the ICU.	HR and BP dynamics across multiple time scales are independent predictors of sepsis, even after adjustment for commonly measured clinical values and patient demographics and comorbidities.	Early recognition and diagnosis of sepsis has the potential to decrease sepsis-related morbidity and mortality through early initiation of treatment protocols.
18	Systematic review	Examine the application of sepsis screening tools for early recognition of sepsis in general hospitalized patients to: (i) identify the accuracy of these tools; (ii) determine the results associated with its implementation; and (iii) describe the implementation process.	Electronic tools can capture, recognize abnormal variables and activate a real-time alert. However, the accuracy of these tools was inconsistent across studies, with only one demonstrating high specificity and sensitivity. Paper-based, nurse-led screening tools appear to be more sensitive in identifying septic patients, but have only been studied in small samples in specific populations. The care measures process appears to be improved; however, demonstrating better results is more challenging.	Clinicians, researchers, and healthcare managers must consider these findings and limitations when implementing screening tools, research, or policy on recognizing sepsis in hospitalized patients in general.

19	Observational cohort study.	Develop and validate an Artificial Intelligence Sepsis Expert (AISE) algorithm for early prediction of sepsis.	For 12-hour, 8-hour, 6-hour, and 4-hour sepsis prediction, AISE achieved area under receiver operating characteristic (AUROC) in the range of 0.83–0.85. AISE performance in the development and validation cohorts was indistinguishable.	Using real-time ICU data available, AISE can accurately predict the onset of sepsis in an ICU patient 4 to 12 hours before clinical recognition. A prospective study is needed to determine the clinical utility of the proposed sepsis prediction model.
20	Prospective observational study transversal	To evaluate the feasibility, reliability and performance of the SOFA and qSOFA clinical scores recommended by the iSSC, to investigate the recognition and management of sepsis, as well as the treatment outcome and risk factors for unfavorable outcome in the setting of a teaching and referral hospital in Central Ethiopia.	The increased risk of mortality was significantly associated with SOFA level and qSOFA score, Gram-negative bacteremia (compared with Gram-positive bacteremia; 42.9 versus 16.7%), and antimicrobial regimen including ceftriaxone (35.7% versus 19.2%) or metronidazole (43.8% versus 25.0%), but not with increased respiratory rate ( $\geq 22/\text{min}$ ) or decreased systolic blood pressure ( $\leq 100\text{mmHg}$ ). In Gram-negative isolates, extended antimicrobial resistance with expression of extended-spectrum beta-lactamase and carbapenemase genes was common. Among adult patients, the sensitivity and specificity of the qSOFA score for detecting sepsis were 54.3% and 66.7%, respectively.	Established sepsis scores were either of limited applicability (SOFA) or, as in the case of qSOFA, were significantly impaired in their sensitivity and specificity, demonstrating the need for further evaluation and adaptation to local settings. Local antimicrobial resistance statistics are needed to guide antimicrobial therapy calculated to support reduction in sepsis mortality.
21	Systematic review with meta-analysis.	Assess the current evidence base for early sepsis interventions (recognition, empirical antibiotics, and resuscitation) in resource-poor settings in sub-Saharan Africa. Main results: Unselected liberal fluid resuscitation strategies were harmful for patients presenting to hospital with sepsis in sub-Saharan Africa.	Unselected liberal fluid resuscitation strategies have been detrimental to patients presenting to hospital with sepsis in sub-Saharan Africa.	There is an urgent need to develop effective strategies to improve outcomes for adults with sepsis in sub-Saharan Africa.
22	Observational study	To evaluate the appropriateness of diagnostic procedures for recognizing sepsis in emergency services and to estimate associations between diagnostic procedures and antibiotic treatment time, and to estimate associations between antibiotic treatment time and mortality.	Delay or non-completion of these key diagnostic procedures predicted a delay of more than 2.5 hours to antibiotic treatment. Patients who received antibiotics within 1 hour had an observed 30-day all-cause mortality of 13.6% (10.1-17.1), within 2 to 3 hours of admission 5.9% (2.8-9.1) and 4 hours or more after admission 10.5% (5.7-15.3).	Key procedures for recognizing sepsis were delayed or not completed in a substantial proportion of patients admitted to the emergency department with sepsis. Delay or non-completion of major diagnostic procedures was associated with prolonged antibiotic treatment time. This suggests a need for systematic improvement in the initial management of patients admitted to emergency departments with sepsis.

23	Technology Analysis Study, Prospective Observational	To evaluate the performance of currently available sepsis recognition tools in patients referred to an acute ambulatory care unit in the community.	Both NEWS and SIRS were better at predicting the need for escalated care than the qSOFA and NICE criteria in patients with suspected infection.	Acute outpatient clinicians must exercise caution when applying the new criteria endorsed by NICE to determine the need for intravenous therapy and hospital site of care. NICE criteria underperform when compared to NEWS and SIRS and new-onset confusion were prevalent in patients aged $\geq 85$ years without infection.
24	Monocentric retrospective cohort study	To evaluate whether lymphocyte subsets can be useful in predicting hospital mortality in septic patients.	Total lymphocyte, CD4 T cell, CD8 T cell, and B cell counts were found to be significantly lower in deceased patients than in survivors. When a dichotomous threshold of $< 400/\mu\text{L}$ for CD4 T cells as the dependent variable was considered in multivariate models, age; female sex, qSOFA and CD4 T cells $< 400/\mu\text{L}$ were the independent predictors.	In conjunction with biomarkers routinely determined to predict prognosis in sepsis, CD4 T lymphocytes, measured at hospital admission, may be useful in identifying patients at increased risk of in-hospital death.
25	Retrospective observational study	Compare time to identification of systemic inflammatory response syndrome criteria (SIRS/Sepsis-2), sepsis-related organ failure assessment criteria (SOFA/Sepsis-3), and quick-SOFA criteria (qSOFA) using registry data electronic health system (EHR).	There were 9,087 patients (54.7%) who identified SIRS-first a median of 26 minutes after ED presentation (IQR 0.109 minutes), with 83.1% identifying SOFA criteria a median of 118 minutes later (IQR 44,401 minutes).). There were 7,037 patients (42.3%) who identified SOFA-first a median of 113 minutes after ED presentation (IQR 60,251 minutes). qSOFA diagnostic criteria were met in 46.4% of patients a median of 351 minutes post-ED presentation (IQR 67.1,165 minutes).	SIRS and SOFA initially identified distinct populations. The use of SIRS resulted in early identification of sepsis from the EHR in $> 50\%$ of patients. Using SOFA alone may delay identification. The use of SIRS alone can lead to non-identification of sepsis, presenting it as acute organic dysfunction. Thus, a combination of inflammatory (SIRS) and organ dysfunction (SOFA) criteria may improve timely EHR-based identification of sepsis. SIRS and SOFA initially identified distinct populations. The use of SIRS resulted in early identification of sepsis from the EHR in $> 50\%$ of patients.
26	Retrospective, international study, Sapphire	To evaluate the effectiveness of the Nefrocheck test (measurement of two biomarkers metalloproteinases-2 and insulin-like growth factor-binding protein) in diagnosing acute renal failure in patients with subclinical sepsis.	Thirty-day mortality was 23% for patients who developed stage 2-3 acute kidney injury within the first 3 days, compared with 14% without stage 2-3 acute kidney injury. However, this difference was greater in the infection without sepsis group. Using a (tissue inhibitor of metalloproteinases-2) $\times$ (insulin growth factor-binding protein 7) cutoff of 2.0 units, 14 patients (11.7%) in the infection/no sepsis group tested positive, of whom 10 (71.4%) developed stage 2-3 acute kidney injury. The positive test result occurred a median of 19 hours (interquartile range, 0.8–34.0h) before acute kidney injury as manifested by serum creatinine or urine output.	Use of the urinary test (tissue metalloproteinases-2 inhibitor) $\times$ (insulin-like growth factor-binding protein 7) can identify acute kidney injury in patients with infection, possibly helping to detect sepsis, almost a day before kidney injury acute be apparent by clinical criteria.

27	Observational study	To find the most effective tool in predicting shock in patients compared to other parameters such as brain natriuretic peptide, lactate, IVC-VI inferior vena cava variation index and extravascular lung water index.	The correlation of brain natriuretic peptide value, lactic acid value, IVC-VI, pulmonary extravascular water index and IVC SCI in patients ill with septic shock has been shown. Positive correlation was observed in BNP value, lactic acid value, IVC-VI, EVLWI and IVC SCI ( $r=0.447$ , $p=0.013$ ; $r=0.484$ , $p=0.007$ ; $r=0.423$ , $p=0.023$ ; $r=0.638$ , $p<0.001$ ; $r=0.599$ , $p<0.001$ ; respectively). However, SCI and EVLWI showed a stronger correlation with SOFA than the others. SCI of CVI, estimated by trans abdominal ultrasound, was more accurate than other commonly used non-invasive predictors. EVLWI, as an accurate and classical predictor, was an invasive predictor. IVC's SCI was faster, more practical and safer than the other.	SCI of CVI was faster, more convenient, and safer than other commonly used noninvasive predictors. Early recognition and diagnosis of sepsis can improve patient outcomes.
28	Prospectively collected cohort study	To investigate whether a single initial determination of procalcitonin (PCT) or C-reactive protein (CRP) in plasma can predict proven sepsis in critically ill patients with positive criteria for Sepsis-3. And also whether a decline in PCT or serial CRP can predict the outcome in 28-day mortality.	Not a single PCT or PCR on admission was able to discriminate proven from unproven sepsis. Furthermore, neither a decline from baseline to day 5 PCT nor CRP could predict 28-day mortality.	PCT and PCR on admission were not able to distinguish patients with proven sepsis from critically ill patients positive for Sepsis-3 criteria. A 5-day decline in PCT and CRP was unable to predict 28-day mortality.
29	Technology Analysis Study	To investigate the connection between the structure of HR and BP time series, captured by quantifying the structure of their corresponding network representation, and early signs of sepsis.	Features derived from a multiscale heart rate and blood pressure time series network have been observed to provide approximately 20% improvement in area under receiver operating characteristic (AUROC) for four hours ahead of predicted sepsis relative to indices. traditional heart rate entropy values (0.78 versus 0.66). The results indicate that this improvement is attributable to both the improved network construction method proposed here and the information incorporated into the higher-order interaction of heart rate and blood pressure time series dynamics.	Predicting the onset of sepsis before clinical recognition will allow for meaningful early interventions (e.g., administration of antibiotics and fluids), which have the potential to decrease sepsis-related morbidity, mortality, and healthcare costs.

30	Retrospective cohort study	Develop a triage-based algorithm and treatment order sets with the goal of improving the quality of care for all patients with sepsis presenting to our emergency department (ED).	There were 346 pre-intervention patients and 270 post-intervention patients. We significantly improved all process measures, including the median antibiotic time by 60 min ( $P = 0.003$ ) and the proportion of patients receiving fluid resuscitation (64.7% vs. 94.4%, $P < 0.001$ ). There was no significant difference in the number of patients admitted to the ICU ( $P = 0.14$ ). The median ICU stay was shorter in the post-intervention group [2.0 days (interquartile range (IQR) 1.0–4.5 days) vs. 5.0 days (IQR 1.5–10.8 days), $P = 0.04$ ], and there was no difference in in-hospital mortality between groups ( $P = 0.27$ ).	A sepsis screening tool based on screening itself has been shown to result in faster and more consistent delivery of care, with a significant improvement in initial resuscitation measures.
31	Meta-analysis study	To evaluate the diagnostic and prognostic value of protein C (PC) as a biomarker for sepsis in adults.	Pooled analysis demonstrated moderate certainty of evidence that PC levels were less reduced in sepsis survivors compared to non-survivors (6 studies, 741 patients, SMD = 0.52, 95% CI 0.24–0.81, $p = 0.0003$ , $I^2 = 55\%$ ) and low certainty of evidence that PC levels were less reduced in septic patients without disseminated intravascular coagulation (DIC) compared to those with DIC (3 studies, 644 patients, MDS = 0.97, 95% CI 0.62–1.32, $p < 0.00001$ , $I^2 = 67\%$ ). CP could not be evaluated as a diagnostic tool due to heterogeneous control populations across studies.	The study demonstrates that PC levels were significantly higher in sepsis survivors compared to non-survivors and patients with sepsis but without disseminated intravascular coagulation (DIC). Assessment is limited by high RoB in included studies and poor reporting of the sensitivity and specificity of CP as a biomarker of sepsis. Future studies are needed to determine the sensitivity and specificity of CP to identify its clinical significance as a biomarker for early recognition of sepsis.
32	Retrospective monocentric cohort study	To evaluate whether lymphocyte subsets can be useful in predicting hospital mortality in septic patients.	Total lymphocyte, CD4 T cell, CD8 T cell, and B cell counts were found to be significantly lower in deceased patients than in surviving patients. In univariate analyses, CD4 T cells/ $\mu\text{L}$ (OR 0.99 for each incremental unit, 95% CI 0.99–1.10, $p < 0.0001$ ), age (OR 1.06, 95% CI 1.04–1.09, $p < 0.0001$ ), procalcitonin (OR 1.01, 95% CI 1.01–1.02, $p < 0.0001$ ) and female gender (OR 2.81, 95% CI 1.49–5.28, $p = 0.001$ ) were associated with in-hospital mortality. When a dichotomous threshold of $< 400/\mu\text{L}$ for CD4 T cells as the dependent variable was considered in multivariate models, age (OR 1.04; 95% CI 1.01–1.09, $p = 0.018$ ); female sex (OR 3.18; 95% CI 1.40–7.20, $p = 0.006$ ), qSOFA (OR 4.00, 95% CI 1.84–8.67, $p < 0.001$ ) and CD4 T cells $< 400/\mu\text{L}$ (OR 5.3; 95% CI 1.65–17.00, $p = 0.005$ ) were the independent predictors.	In conjunction with biomarkers routinely determined to predict prognosis in sepsis, CD4 T lymphocytes, measured at hospital admission, may be useful in identifying patients at increased risk of in-hospital death.

33	Systematic review and meta-analysis	Evaluate the performance of new machine models that predict sepsis in real time.	For the prediction of sepsis, the accuracy of the diagnostic test assessed by AUROC ranged from 0.68–0.99 in the ICU, to 0.96–0.98 in the hospital and 0.87 to 0.97 in the emergency room. Varying definitions of sepsis limit pooling of performance across studies. Only three articles implemented models clinically with mixed results. In multivariate analysis, temperature, laboratory values, and model type contributed most to model performance.	This systematic review and meta-analysis show that, in retrospective data, individual machine learning models can accurately predict the onset of sepsis ahead of time. Although they present alternatives to traditional scoring systems, the heterogeneity between studies limits the evaluation of grouped results. Systematic reporting and clinical implementation studies are needed to bridge the gap between the bytes and the bedside.
34	Prospective study	Compare the performance of qSOFA, systemic inflammatory response syndrome (SIRS) criteria, National Early Warning Score (NEWS) and formal screening with the Emergency Severity Index (ESI) algorithm to identify patients with sepsis and predict adverse outcomes upon arrival at an emergency department (ED) cohort of all participants.	A total of 2,523 cases were included in the analysis and 39 (1.6%) had sepsis as the primary outcome. The area under the curve for sepsis was 0.79 (95% confidence interval [CI] 0.71-0.86) for qSOFA, 0.81 (95% CI 0.73-0.87) for SIRS, 0.85 (95% CI 0.77-0.92) for NEWS and 0.77 (95% CI 0.70-0.83) for ESI.	The qSOFA offered high specificity for predicting sepsis and adverse outcomes. However, its low sensitivity does not support widespread use as a screening tool for sepsis. NEWS outperformed qSOFA in predicting adverse outcomes and sepsis screening.

**Table 2:** Research design, objective, main results and conclusions of the articles selected for the integrative review (Macaé, Rio de Janeiro, Brazil, 2022)



defined the criteria for early diagnosis of organ dysfunction resulting from sepsis as: a score  $\geq 2$  according to the SIRS criteria or a score  $\geq 2$  according to the SOFA criteria. This demonstrates that the diagnostic criteria for organic dysfunction caused by sepsis are not consensual in all scientific literature, so each author can adopt a different approach, allowing room for different interpretations.

Despite this, it is clear that there is still an important difficulty in early detection of sepsis, as unlike a syndrome with signs and symptoms visible on physical/clinical examination, to diagnose it it is often necessary to carry out laboratory tests, the results of which take considerable time to obtain. This is also due to the fact that to diagnose sepsis early, up-to-date clinical measures are necessary, which are more likely to be available when the patient already has some suspicion of infection. And as discussed in the studies obtained in this research (Husabø, Gunnar et al, 2020; Crouser, Elliott D et al, 2019), each hour of delay in treatment is responsible for a significant worsening of the patient's prognosis.

Currently, the gold standards for diagnosing sepsis indicated by the main guidelines correspond to SOFA and qSOFA. SOFA is only used to characterize the syndrome and its use for patient management purposes is not recommended. Despite being the gold standard in detecting the syndrome, it has limitations in its application as it depends on laboratory tests to meet its criteria, which causes delays in the diagnosis of this important syndrome. qSOFA, in turn, is more practical and has greater applicability, as its parameters are easily measured in clinical practice. This score is most used to predict mortality of patients outside the ICU, as a criterion for clinical screening for the diagnosis of sepsis (SILVA, L.M.F et al, 2021).

Other scoring methods for sepsis are the prior evaluation of patients who already have

an infection and who have a high chance of developing unfavorably, such as patients who meet the criteria for Systemic Inflammatory Response Syndrome (SIRS). However, the applicability of the SIRS criteria may present many obstacles given their poor specificity, as signs of an inflammatory response may be present in several other clinical conditions in addition to sepsis (VERBOOM, Diana M et al, 2019). Furthermore, the National Early Warning Score (NEWS) has been used in some countries to evaluate and monitor patients, which is a scoring method that uses parameters such as temperature, heart rate, systolic blood pressure, respiratory rate, oxygen saturation, supplementation oxygen supply and central nervous system response (ABOTT, T.E.F et al., 2018).

The Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021 points out that qSOFA, despite being more specific, is less sensitive when compared to cases in which patients have two out of four SIRS criteria for early identification of infection, also strongly recommending that qSOFA not be used individually as a screening tool.

In article number 25 in table 2, it is concluded that the use of SOFA alone can delay the identification of sepsis, while the isolated use of SIRS can lead to non-identification of sepsis. Article number 34, on the other hand, concludes that qSOFA offered high specificity for predicting sepsis and adverse outcomes. However, its low sensitivity does not support widespread use as a screening tool for sepsis. Another important fact is that both the NEWS and the SIRS criteria outperformed the qSOFA in predicting adverse results and sepsis screening, as demonstrated in study number 23. Thus, it can be seen that score-based diagnostic methods do have their applicability, but they are not sufficient to support the widespread use for determining

the syndrome due to their low scope of recognition of all the pathological factors that are presented in this clinical picture.

## BIOCHEMICAL MARKERS

Studies presented in articles numbers 4, 8, 24 and 32 were conducted with the new biomarkers in an isolated and composite manner in an attempt to overcome the limitations of the lack of sensitivity and specificity of the criteria commonly used for diagnosing sepsis. The results obtained between the two forms of testing indicate that, together with the biomarkers routinely determined to predict the prognosis in sepsis, CD4 T lymphocytes, measured at hospital admission, can be useful in identifying patients at greater risk of death intravenously. -hospital. It was also observed that the diagnostic efficacy of International Normalized Ratio (INR) was more significant than that of Neutrophil-Lymphocyte Count Ratio (NLCR), platelets (PLT) and qSOFA. The combination of biomarkers can improve the diagnosis of bacterial sepsis seen in the most severe patients, but in conditions of less severe sepsis neither NLCR or PCT alone exhibit equivalent performance.

Even with the recognition of some biochemical markers, which are generally quite sensitive in the presence of sepsis, they are not so specific to diagnose the infection as a cause of changes in their values, nor to identify which sick patients will develop other complications (SINGER, M., 2019).

## TECHNOLOGIES IN DEVELOPMENT

According to the Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021, new computational models for predicting sepsis can improve currently available screening tools. The clustered area under the

receiving operating curve (SAUROC meta-analytic curve) has been shown to be more effective for predicting sepsis than traditional screening tools such as SIRS, MEWS, and SOFA. Despite the variety in sensitivity and specificity across all screening tools, it is important to use these technologies to ensure early identification of sepsis and consequently rapid intervention. Despite this, the need to improve the accuracy of diagnoses made by computer learning is still observed in recent studies, as the accuracy of these tools has proven to be inconsistent between studies. The same applies to technologies that have not yet been validated, since their unique uses do not guarantee diagnostic accuracy. Therefore, what is recommended in all cases is the combination of more than one assessment method to determine the diagnosis.

According to the results of article 8 in this research, the International Normalized Ratio (INR) is a promising and easy-to-obtain marker for diagnosis, and can be used as one of the indicators for early screening of non-pulmonary infectious sepsis. Also present in the results of the article "Presepsin level in predicting patients' in-hospital mortality from sepsis under sepsis-3 criteria", the marker that presented the greatest accuracy in predicting the prognosis of sepsis was pre-sepsin, while the other markers were mostly used for the actual recognition of sepsis in the patient. However, none of these two parameters have been consolidated to date, which explains why they are not found in current guidelines. Finally, article 3 of this research discusses the need for new targets and predictive biomarkers with the aim of improving both the diagnosis and prognosis of sepsis.

## FINAL CONSIDERATIONS

According to the findings of this research, many studies have been carried out in search of new biochemical markers that can indicate

and determine the diagnosis of sepsis and its possible complications. Among them, we can mention C-reactive protein, procalcitonin, CD4 T lymphocytes, lactate, pre-sepsin, monocytes and prothrombin time, in addition to the usual biomarkers for investigating sepsis, such as bilirubin, platelets, creatinine and urea.

Screening tools based on scores applied by nurses proved to be relatively sensitive in identifying septic patients (ALBERTO, Laura et al, 2017). This way, it is possible to recognize why the Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021 strongly recommends not using qSOFA compared with SIRS, NEWS or MEWS criteria as a

single screening tool. for sepsis or septic shock. Despite their flaws, these diagnostic methods, when used together, can be valid and complementary for the early prediction of sepsis. However, with this research it is clear that they all have limitations and health professionals who use them need to be aware of this and look for ways to overcome these limitations to reach an accurate diagnosis.

Analyzing the content of the studies brought here, it is clear that there are several studies showing great interest in new searches to identify one or more biochemical markers that are characteristic of sepsis, as there is a consensus that the current methods used to its detection still fails in terms of sensitivity and specificity.

## REFERENCES

1. INSTITUTO LATINO AMERICANO DE SEPSE. Implementação De Protocolo Gerenciado De Sepse: Protocolo Clínico Adulto. Instituto Latino Americano de Sepse, São Paulo, 2018. Disponível em: <<https://ilas.org.br/assets/arquivos/ferramentas/protocolo-de-tratamento.pdf>> .Acesso em: 28 fev. 2022.
2. INSTITUTO LATINO AMERICANO DE SEPSE. Sepse: um problema de saúde pública. Brasília. Conselho Federal de Medicina, 2016. Disponível em: <<https://ilas.org.br/assets/arquivos/ferramentas/livro-sepse-um-problema-de-saude-publica-cfm-ilas.pdf>>. Acessado em: 28 fev. 2022.
3. RHODES, A., Evans, L.E., Alhazzani, W. *et al.* Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med* **43**, 304–377 (2017). <https://doi.org/10.1007/s00134-017-4683-6>. Disponível em: < <https://link.springer.com/article/10.1007/s00134-017-4683-6#citeas>>. Acessado em: 28 fev. 2022.
4. SINGER, Mervyn. “Biomarkers for sepsis – past, present and future.” *Qatar Medical Journal* vol. 2019,2 8. 7 Nov. 2019. Disponível em: <<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6851944/>>. Acessado em: 5 mar. 2022.
5. MD., Mohaimenul Islam *et al.* Prediction of sepsis patients using machine learning approach: A meta-analysis. *Computer Methods and Programs in Biomedicine*, v.170, 2019, pages 1-9. Disponível em: <<https://www.sciencedirect.com/science/article/abs/pii/S016926071831602X?via%3Dihub>> Acessado em: 6 mar. 2022.
6. ABOU, T.E.F *et al.* Pre-hospital National Early Warning Score (NEWS) is associated with in-hospital mortality and critical care unit admission: A cohort study. *Annals of Medicine and Surgery*, v.27, 2018, p. 17-21. Disponível em: < <https://www.sciencedirect.com/science/article/pii/S2049080118300116>>. Acessado em: 7 mar. 2022.
7. SILVA, L.M.F *et al.* Desempenho de escores na predição de desfechos clínicos em pacientes admitidos a partir de emergência. *Revista Latino-Americana de Enfermagem*. Ribeirão Preto. Vol. 29, 2021, p. 1-10. Disponível em: < <https://www.scielo.br/j/rlae/a/PCtjkZ4rRjkSS8xX5JTRWHD/?format=pdf&lang=pt>>. Acessado em: 5 mar. 2022.
8. EVANS, Laura *et al.* Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. *Critical Care Medicine*. November 2021, v. 49, Issue 11, p e1063-e1143. Disponível em: <[https://journals.lww.com/ccmjournal/fulltext/2021/11000/surviving\\_sepsis\\_campaign\\_\\_international.21.aspx](https://journals.lww.com/ccmjournal/fulltext/2021/11000/surviving_sepsis_campaign__international.21.aspx)>. Acessado em: 3 mar. 2022