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INTERSECTIONS BETWEEN ARTIFICIAL INTELLIGENCE (AI) AND SEPSIS: AN INTEGRATIVE REVIEW

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Abstract: Objectives: To conduct an integrative review of the literature to investigate the impact of artificial intelligence (AI) on the clinical management of sepsis. **Methods:** Databases such as PubMed/MEDLINE and LILACS were used, and the search for articles was guided by the question: what is the contribution of AI to the detection and/or treatment of sepsis? **Results:** Of the 11 articles selected, the fundamental role of *machine learning* in the development of predictive models for the identification of early signs of sepsis stood out, resulting in improvements in interventions and prognoses. In addition, AI was applied in patient monitoring systems, such as Robô Laura™, optimizing clinical processes. **Conclusions:** AI plays a significant role in advancing the clinical management of sepsis, offering innovative perspectives for diagnosis, treatment, and prognosis.

Keywords: Sepsis; Machine Learning; Algorithms

Introduction

Sepsis is a syndrome in which an infection causes an imbalance in the patient's immune response, damaging several vital organs[1]. In Brazil, the number of deaths from sepsis in 2002 was 982,294, while in 2010 this number was 1,131,761, representing an increase of 149,467 deaths[2]. Between 2001 and 2010, hospital mortality from sepsis reached values between 17% and 26%[3] .

Early prediction and intervention in sepsis are fundamental to successful treatment, in addition to generating economic impacts, as its treatment requires advanced equipment, expensive medication, and qualified medical care, placing a burden on the public and private sectors[1,4].

The term artificial intelligence (AI) emerged in 1950 and refers to an area of computer science based on algorithms that simulate human cognitive functions[5]. After 2012, due to the increase in data volume, computing power, and the development of new algorithms, areas of AI such as machine learning (*ML*), deep learning, evolutionary computing, computer vision, and natural language processing evolved. *ML* is widely used in sepsis.

To date, there is no reliable diagnostic test or direct treatment for sepsis. As AI applications in medicine continue to emerge, some clinical decisions will be aided by so-called "intelligent" machines, which will improve patient diagnosis, treatment, and prognosis. Improvements in treatment would include the choice of better antimicrobial therapy protocols and hemodynamic management of the patient.

The objective of this study was to conduct an integrative literature review to seek evidence of AI's contributions to the clinical management of sepsis.

Methods

Integrative reviews consist of analyzing a set of publications in order to group and synthesize the results of a study. The steps of this review were: I) selection of guiding questions; II) selection of studies and III) characterization of them; IV) critical analysis of the included studies; V) interpretation and discussion of the results; VI) presentation of the review[7].

The question of the integrative literature review was: what is the contribution of artificial intelligence (AI) to the detection and/or treatment of sepsis? For the review, a search was conducted in the databases on March 20, 2024. The databases chosen were PubMed/MEDLINE and the Latin American Literature in Health Sciences (LILACS), as they are widely accessed by the medical community.

Scientific articles from primary research published in the last three years (January 1, 2021, to January 1, 2024) in English, Portuguese, and Spanish were selected. Scientific review articles of any type, book chapters, monographs, course completion papers, master's dissertations, and any type of thesis were excluded. Articles cited in more than one database were also excluded.

The Boolean operators AND and OR helped refine the database search, as they link subject descriptors during the search (Soares)[7]. To retrieve the scientific articles that best answered the research question, the search was performed using the following subject descriptors (searched at https://decs.bvsalud.org/) and their synonyms: ((intelligence) AND (artificial)) AND (sepsis); ((machine) AND (learning)) AND (sepsis); ((deep) AND (learning)) AND (sepsis).

After the search and according to the inclusion and exclusion criteria, 21 articles were selected for analysis, and after analyzing the abstracts, 11 were selected for full reading. After reading, the data were categorized and tabulated.

Results

Of the selected articles (n=11), two were produced in Brazil (18.18%), while six were produced in China (54.5%) and three articles were produced in Singapore, Japan, and the Netherlands (27.28%). Regarding the type of study, theoretical and descriptive research predominated (63.63%), with 36.37% being experimental and descriptive research (Table 1).

Discussion

The studies selected and analyzed in this integrative literature review highlighted some contributions of informatics to sepsis. One of them is the attempt to obtain better predictive factors for diagnosing and intervening in sepsis. In the search for predictive factors, the use of AI was fundamental, with *Machine Learning* standing out [8-18].

Some studies were conducted using databases. The advantage is having access to a large amount of data, i.e., the data set for training and validation makes the analysis more robust [8,9,12,13,17].

Early identification and treatment of sepsis represent a challenge that requires the continuous emergence of AI applications. Predictive models are fundamental and can be based on several factors. A study conducted in China suggests that the most significant factors, after using the *Random Forest* method in a sepsis prediction model, are (in descending order): neutrophils (%), D-dimer, eosinophils (%), lymphocytes (%), and albumin[12] .

Some metabolites may be altered in sepsis. One study determined that the main differentially expressed metabolites were those related to the metabolism of phenylalanine, tyrosine, glycine, serine, threonine, arginine, and proline. *ML* algorithms were used to identify these meta-

Author(s) / Year / Location	Type of study / Objective(s) / Sample	Contributions of the study
Kalil et al. 2018 Brazil	Theoretical and descriptive research. To assess the impact of implementing a cognitive robot in identifying and caring for patients at risk of sepsis in a clinical-surgical setting. A database was used with the vital signs history of 60 patients admitted in two periods: April to September 2016 and October 2016 to March 2017.	Although the model does not appear to have a positive impact on the clinical management of patients, it may encourage new research with a larger sample size, demonstrating its beneficial potential in the clinical approach to sepsis (8).
Doorn et al. 2021 Netherlands	Theoretical and descriptive research. Develop machine learning models to predict mortality in emergency room patients in the emergency room with sepsis and compare them with internal medicine physicians and clinical risk scores. Laboratory and clinical data from 1,344 patients with signs of sepsis, obtained in the first two hours of care, were used. They were divided into development (n = 1,244) and validation data (n = 100).	The machine learning models outperformed internal medicine physicians and clinical risk scores in predicting mortality at 31 days. These models are a promising tool to assist in risk stratification in patients arriving the emergency department with sepsis (9).
Kudo et al. 2021 Japan	Theoretical and descriptive research. Examine the latent phenotypes of sepsis with coagulopathy and the associations between thrombomodulin treatment and mortality at 28 days and during hospitalization for each phenotype. The sepsis phenotypes from the JSEP-TIC-DIC study (n = 3,195) and the Tohoku Sepsis Registry (n = 499) (n = 499) and validated the phenotypes using the FORECAST sepsis study (n = 1,184).	The effects of thrombomodulin treatment varied across sepsis phenotypes. This finding will facilitate future trials with thrombomodulin (10).
Scherer et al. 2021 Brazil	Experimental and descriptive research. Analyze critical alarms predictive of clinical deterioration/sepsis for clinical decision-making clinical decision-making in hospitalized patients. Sixty-one hospitalized patients over the age of 18 were evaluated.	*Machine learning* models can accelerate assertive clinical decision-making by nursing staff (11).

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Wang et al. 2021 China	Theoretical and descriptive research. Develop an AI algorithm that can predict sepsis early. A database of 17,005 patients treated in intensive care units (ICUs) was used After exclusion criteria, 4,449 patients were selected, of whom 3,539 developed sepsis.	The established machine learning-based model demonstrated good predictive ability in Chinese patients with sepsis (12).
Hong et al. 2022 China	Theoretical and descriptive research. To construct a predictive model for sepsis in patients with upper urinary tract stones. Between January 2016 and January 2020, 2,387 patients diagnosed with upper urinary tract stones were selected, and after applying the exclusion criteria, 1,716 patients were selected and divided into two groups: training set (n=1,214) and test set (n=502).	This was the first study using artificial neural networks to estimate the risk of sepsis for patients with upper urinary tract stones, based on ultrasound and urinalysis (13).
Li et al. 2022 China	Experimental and descriptive research. Identify prognostic factors in patients with invasive *Candida* infection, concomitant with bacterial infection in the circulation. A total of 246 patients with invasive *Candida* infection complicated by bloodstream infection were included.	It was determined that the main predictors of death are serum creatinine, age, length of hospital stay, stay in the ICU during hospitalization, serum albumin level, C-reactive protein, neutrophil count, procalcitonin, and total bilirubin (14).
Liaw et al. 2023 Singapore	Experimental and descriptive research. Evaluate the effectiveness of AI-assisted physician versus controlled virtual reality, by humans in training nursing students for sepsis care. Participants were 64 nursing students	AI-driven doctors are comparable to human-controlled virtual reality simulations controlled by humans in sepsis care (15).

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Liu et al. 2023 China	Theoretical and descriptive research. To build predictive models for sepsis risk in patients with acute pancreatitis. Data were collected from the Medical Information Mart for Intensive Care III (MIMIC III) database between 2001 and 2012 and from MIMICIV between 2008 and 2019. A total of 1,930 patients were selected and, after exclusion criteria, remaining 1,672 patients were divided into two sets: training (n=1,338) and test (n=334).	When compared to logistic regression models, SOFA, qSOFA, SAPS II, SIRS, and BISAP, the Machine Learning (GBDT) model performed better in predicting sepsis in patients with acute pancreatitis (16).
Pan et al. 2023 China	Theoretical and descriptive research. Develop machine learning models based on Sequential Organ Failure Assessment (SOFA) components to predict early in-hospital mortality in ICU patients with sepsis and evaluate the performance of the model. The MIMIC-IV database (Version 1.0) was used, which is publicly available and has more than 40,000 ICU patients admitted to the ICUs of Beth Israel Deaconess Medical Center between 2008 and 2019. From this database, 35,010 patients were selected, and after exclusion criteria, 23,889 patients were used.	The two machine learning-based models (logistic regression and Naive Bayes models) built using SOFA components can be used to predict in-hospital mortality in septic patients admitted to the ICU (17). Logistic Regression and Naive Bayes models) built based on SOFA components can be used to predict in-hospital mortality of septic patients admitted to the ICU (17).
She et al. 2023 China	Experimental and descriptive research. Identify the main metabolites potentially associated with the accurate diagnosis and prognosis of sepsis. Between December 2021 and April 2022, a total of 30 patients with sepsis were recruited from the intensive care unit. In addition, 15 healthy volunteers enrolled to form the control group.	The study used metabolomics and machine learning to identify metabolites associated with the diagnosis and prognosis of sepsis (18).

Table 1 – Presentation of the reviewed studies, according to authors, year, location, type of study, objectives, sample, and main contributions to the state of the art.

bolites: *support vector machine* (SVM) and *random forest* (RF). Identification is useful in the pharmacological blockade of these metabolites to increase patient survival[18].

In some situations, we can observe the effect of a treatment on the prognosis of sepsis. Thrombomodulin can be used to prevent intravascular coagulation. One study separated the data from a database into *clusters*, using *ML* to form the *clusters* based on parameters associated with blood coagulation (platelet count, D-dimer, among others). It was observed that recombinant thrombomodulin can benefit patients with severe coagulopathy. Identify patients for whom a therapy will have a beneficial effect on precision/adaptive medicine in critical care[10] .

One of the studies used the Laura™ Robot, which incorporates an *ML* algorithm that analyzes hospital vital signs in real time and generates a patient deterioration index. Two parameters were analyzed, six months before and six months after the introduction of the technology: the average time to antibiotic prescription from the first identified sign of infection (with or without sepsis) and the average time to care (ATC), which measures the entry of any patient data into the electronic medical record (EMR). There was a significant difference only in TMA, which decreased from 305 to 280 minutes, demonstrating a possible improvement in the team's performance in entering patient data into the EMR[8].

Another study also used the Laura™ Robot to analyze critical alarms predicting deterioration/sepsis for decision-making in the care of patients at risk of sepsis. The Robot scored changes in vital signs and laboratory tests, classifying them by severity. More than 122,000 alerts were analyzed, 0.2% of which required urgent intervention and consequently impacted mortality. *ML* models can accelerate clinical decisions by nurses based on critical alarms, optimizing time and specialized human resources[11].

One of the diseases associated with sepsis is upper tract urolithiasis (UTU). Because it is common, an *ML* model was created to predict the risk of sepsis in patients with UTU. A prediction model was developed using an artificial neural network (ANN), involving eight significant predictors, including gender, age, history of diabetes, body temperature, leukocytes, nitrite, and glucose in urine, and degree of hydronephrosis. The ANN model showed encouraging results in terms of its ability to identify sepsis in UUTS early, based on ultrasound and urinalysis[13].

Invasive *Candida* infection combined with bacterial infection in the bloodstream is common and the leading cause of morbidity and mortality. A *ML* model was used to determine the risk of sepsis in these patients. The main predictors of mortality are serum creatinine level, age, length of stay, ICU stay during hospitalization, serum albumin level, C-reactive protein (CRP), white blood cell count, neutrophil count, procalcitonin (PCT), and total bilirubin level[14] .

Another disease associated with sepsis is acute pancreatitis, and building predictive models is necessary. In addition, it is very important to compare different *machine learning* models, such as *support vector machine* (SVM), *K-nearest neighbor* (KNN), *multi-layer perceptron* (MLP), linear regression, *gradient boosting decision tree* (GBDT), and *adaptive enhancement algorithm* (AdaBoost). The models were evaluated and compared using sensitivity, specificity, positive predictive value (PPV), value negative predictive

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value (NPV), accuracy, and area under the curve (AUC). The GBDT model showed better performance in predicting sepsis than the linear regression model. In addition, the GBDT model was superior to some scores such as the systemic inflammatory response syndrome (SIRS) score, the severity index in acute pancreatitis (BISAP), the sequential organ failure assessment (SOFA), the quick--SOFA (qSOFA), and the simplified acute physiology score II (SAPS II)[16] .

An important index to be determined in sepsis is the mortality rate over a certain period of time, such as 31-day mortality. For this purpose, machine learning models can be developed using laboratory and clinical data. In many cases, the model proves to be superior to physicians and clinical risk *scores* in predicting mortality. However, some limiting factors should be considered, such as using a small database, which may limit, but not disqualify, the results[9] .

ML models can be developed from components used in the assessment of patients with sepsis, such as the Sequential Organ Failure Assessment (SOFA). SOFA helps to predict early hospital mortality in ICU patients with sepsis. One study developed two *ML* models: logistic regression and Gaussian Naive Bayes, based on SOFA components. Both can be used as predictors of hospital mortality in patients with sepsis admitted to the ICU[17].

In some studies, AI was used in the training of healthcare teams, including nursing students. A group of nursing students was randomized to participate in sepsis team training with an AI-controlled physician or with medical students using virtual reality (VR) simulation. It was concluded that AI--controlled physicians are not inferior to human-controlled virtual reality simulations in terms of sepsis care performance and interprofessional communication, which supports the implementation of AI-controlled physicians to increase scalability in sepsis team training[15].

Conclusion

Artificial intelligence (AI) plays a significant role in advancing the clinical management of sepsis. The search for more accurate predictive factors, combined with the ability to process large data sets, enables the development of more reliable predictive models. These models, based on AI algorithms, can identify early signs of sepsis in different conditions, resulting in rapid and effective interventions.

The studies reviewed indicate the potential of AI to improve patient care. The integration of AI algorithms into patient monitoring systems, such as Robô Laura™, has reduced the time to the first antibiotic prescription and improved the efficiency of clinical data recording.

Artificial intelligence can also be used in the training of healthcare teams, as it provides realistic simulations and facilitates interprofessional communication. The implementation of AI-assisted physicians is an innovative approach, ensuring standardized, high-quality care.

AI has made an undeniable contribution to the way we deal with sepsis, offering new perspectives for diagnosis, treatment, and prognosis. However, it is crucial to invest in research in this area to ensure that these technologies are accessible, reliable, and widely adopted in clinical practice, with the ultimate goal of reducing mortality from sepsis.

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