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REVIEW ARTICLE

Artificial intelligence-based techniques for predicting outcomes in COVID-19 patients

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ABSTRACT

Introduction. Currently, extensive research has shown that almost all published prediction models are poorly studied and have significant limitations, leading to their predictive performance often being overestimated. Additionally, there is still no universally accepted scoring system, primarily due to the need for adaptation to heterogeneous patient samples (including patient numbers, clinical profiles, and risk factors) and/or ongoing differences in the organization of healthcare systems across various countries.

Materials and methods. This is a narrative literature review. A bibliographic search was conducted in *the PubMed, Hinari, SpringerLink, National Center for Biotechnology Information*, and *Medline* databases. Articles published between 2000 and 2024 were selected based on keyword combinations such as “artificial intelligence”, “prediction model”, “algorithm”, “machine learning”, and “COVID-19”. Information on machine learning predictive models was selected and processed to identify characteristics that can be used to predict diagnosis, severity, length of hospital stay, ICU admission, treatment, vaccination, and mortality in COVID-19 patients. After processing the data according to the search criteria, 125 full-text articles were identified. The final bibliography includes 52 relevant sources, which were considered representative of the literature on this synthesis article topic.

Results. Artificial intelligence techniques are increasingly being used to predict outcomes in COVID-19 patients, particularly in estimating mortality among individuals infected with SARS-CoV-2, which can rapidly and effectively support clinical decision-making. According to the analysis of multiple studies, strong predictors of mortality in COVID-19 patients include advanced age, male gender, comorbidities, reduced levels of calcium, albumin, red blood cells, and oxygen saturation, as well as lymphopenia, elevated blood urea nitrogen, creatinine, lactate dehydrogenase, D-dimers, neutrophils, interleukin-6, procalcitonin, bilirubin, ferritin, aspartate aminotransferase, and troponin.

Conclusions. Artificial intelligence techniques provide potential advantages over conventional assessment methods. The information obtained from machine learning and deep learning algorithms, including easily accessible and interpretable data, can assist healthcare workers in making accurate decisions for the appropriate and timely care of COVID- 19 patients. This can improve patient outcomes, reduce the burden on healthcare systems, and ultimately decrease mortality rates.

Keywords: artificial intelligence, predictive model, algorithm, machine learning, deep learning, COVID-19.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

Currently, many large-scale studies show that almost all prediction models based on artificial intelligence are not well-researched and have significant limitations, meaning their reported predictive performance is often overestimated.

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The research hypothesis
The contribution of machine learning techniques to medical practice is an emerging subject in the medical literature, with different opinions on their utility. Analyzing and reviewing relevant up-to-date articles will provide a detailed overview of predictive models based on *machine learning*, which use computer algorithms to assess patient health risks, manage clinical care, and predict mortality in COVID-19 patients, including those admitted to Intensive Care Units within the local healthcare system.

The novelty added by manuscript to the already published scientific literature
The article summarizes the latest international publications to identify a practical machine-based scoring system capable of predicting disease severity and risk of death, with the aim of reducing mortality rates.

Introduction

The rapid progression and worsening of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) highlight the need for early identification of high-risk patients, as well as the prompt and effective implementation of support measures to improve prognosis. Detecting patients at high risk of death can improve clinical outcomes through the rapid and individualized selection of effective treatment methods, resource optimization, and higher quality of healthcare delivery [1-6].

According to study results, *machine learning* and *deep learning* algorithms are highly effective in predicting mortality associated with coronavirus disease 2019 (COVID-19) [7, 8]. The indicators obtained were more effective compared to conventional statistical models (regression analysis, factor analysis, discriminant analysis) and traditional scoring systems (SOFA, SAPS-II, CURB-65, APACHE-II, APACHE-IV) [2, 3, 9-12].

Currently, extensive research shows that nearly all published prediction models are poorly studied and have significant limitations, leading to their predictive performance often being overestimated. Additionally, there is still no universally accepted scoring system, mainly due to the need for adaptation to heterogeneous patient samples (including patient numbers, clinical profiles, and risk factors) and/or ongoing differences in the organization of healthcare systems across various countries [13-16].

Artificial intelligence applications, especially machine learning and deep learning algorithms, have great potential to support healthcare professionals in decision-making, predicting complications and mortality in hospitalized patients, including those admitted to intensive care units (ICUs). Medical validation of predictive models should be performed by clinical experts, and the most effective models can be implemented in different hospitals and healthcare institutions [14, 17-19].

In this context, the **purpose** of this article is to present a synthesis of the most recent data regarding the effectiveness of *machine learning* algorithms and artificial intelligence in predicting mortality among COVID-19 patients.

Material and methods

To achieve the study purpose, an initial search was conducted for specialized scientific publications identified through Google Search and the *PubMed, Hinari (Health Internet Work Access to Research Initiative), SpringerLink, National Center for Biotechnology Information*, and *Medline* databases. The selection criteria for articles included state-of-the-art data on machine learning-based mortality prediction models using the following keywords: "artificial intelligence", "prediction model", "algorithm", "machine learning", "deep learning", and "COVID-19", which were used in various combinations to increase search efficiency.

For the advanced selection of bibliographic sources, the following filters were applied: full-text articles, articles in English, and articles published between 2000 and 2024. After a preliminary analysis of the titles, original articles, editorials, narrative reviews, systematic reviews, and meta-analyses containing relevant information and current concepts regarding the application of machine learning algorithms and artificial intelligence in the diagnosis, prediction of severity, and mortality risk in patients with COVID-19 were selected. Additionally, a search of the reference lists of the identified sources was conducted to identify additional relevant publications that were not found in the initial database search.

The information from the publications included in the bibliography was gathered, classified, evaluated, and synthesized, highlighting the main aspects of the contemporary perspective on the effectiveness of cutting-edge *machine learning* and *deep learning* algorithms, used either separately or in combination, in predicting mortality caused by SARS-CoV-2 infection.

To minimize the risk of systematic errors (bias) in the study, a thorough data search was conducted to identify the maximum number of relevant publications for the study's objectives. Only studies meeting reliability criteria were evaluated, while strict exclusion criteria were employed to remove articles from the present study. Moreover, both studies showing positive results and those not emphasizing the benefits of predictive models were analyzed.

If necessary, additional sources of information were consulted to clarify some concepts. Duplicate publications, articles that did not correspond to the purpose of the article, and those not available for full review were excluded from the list of publications generated by the search engine.

Results

After processing the information identified by the Google Search engine and from databases such as *PubMed, Hinari, SpringerLink, the National Center for Biotechnology Information*, and *Medline,* according to the established search criteria, a total of 125 articles addressing the application of machine learning algorithms and artificial intelligence in the diagnosis, prediction of severity, and mortality risk in COVID-19 patients were found. After an initial review of the titles, 59 articles were considered potentially relevant to this synthesis. Following a thorough review of these sources, 52 publications were ultimately selected as relevant to the stated objective. The final bibliography of the paper included these 52 articles, which were considered representative of the published materials on this synthesis topic.

Publications whose content did not reflect the considered topic, even though they were selected by the search program, as well as articles that were not accessible for free viewing through the *HINARI* database or available in the medical scientific library of the Nicolae Testemițanu State University of Medicine and Pharmacy, were subsequently excluded from the list.

The complexity of severe acute respiratory syndrome SARS-CoV-2 lies in the unpredictable clinical evolution of the disease, which develops rapidly, recording high morbidity and mortality rates. In this context, the identification and use of mortality prognostic models based on *machine learning* and *deep learning* algorithms become mandatory for the purposes of risk stratification, clinical management, and mortality prediction of COVID-19 patients, especially those hospitalized in intensive care units. Therefore, identifying a feasible mortality prediction score based on artificial intelligence techniques represents not only an urgent need for monitoring, predicting outcomes, and prognosis of the disease but also a key factor in reducing mortality rates [20-29].

Predictive models, also known as “prognostic models”, “risk scores”, or “prediction rules”, are developed to assist healthcare providers in estimating the probability or risk of the presence of a condition or disease (diagnostic models) or the occurrence of an event in the future (prognostic models) for the purpose of informing and making appropriate decisions [4, 16, 30].

There are several studies that have shown that traditional risk scores generally underestimate mortality in patients with COVID-19 [31, 32]. Although multiple scores are currently used to predict mortality in patients with COVID-19, there is no universal score to date, and artificial intelligence has been used less than expected for this purpose. However, AI-based methods (*machine learning* and *deep learning*) are increasingly being used to study patient risk stratification in almost all areas of COVID-19 pandemic management. Numerous studies have been conducted to develop computerized predictive models for early disease prediction, diagnosis, severity assessment, progression, the need for ICU admission, and mortality risk evaluation in patients infected with SARS-CoV-2 [18, 25-27, 29, 33].

Firstly, feature classification (or selection or reduction) algorithm is used to pre-process the information to query new features, remove redundant values and unusable data, handle missing values, and select the most important features. SHAP *(SHaPley Additive exPlanations*) and LASSO (Least Absolute Shrinkage and Selection Operator) are most used for this purpose. After pre-processing the information, *machine learning* or *deep learning* algorithms are used to create a predictive model [18, 27, 34-36].

The latest generation of *machine learning* algorithms (*decision tree* – J48, *random forest* – RF, *artificial neural network* – ANN, *K-nearest neighbor* – k-NN, *multilayer perceptron* – MLP, *linear discriminant analysis* – LDA, *naive Bayes* – NB, *extreme gradient boosting* – XGBoost, *adaptive boosting* – AdaBoost, *support vector machine* – SVM, *logistic regression* – LR) and *deep learning* methods (*convolutional neural networks* – CNN, *feedforward neural network* – FNN, *long short-term memory* – LSTM, *autoregressive integrated moving average* – ARIMA, *partial least squares-discriminant analysis* – PLS-DA, *auto-encoder* – AE) are the most commonly used methods. Studies have investigated the effectiveness of these models both individually and in combination for predicting mortality caused by COVID-19 [18, 19, 26, 27, 37-39].

To improve the prognostic model for patients admitted to ICUs, a new strategy is needed that could be easily updated periodically and include the latest clinical data reflecting the local characteristics of each medical institution. Electronic medical records have provided the opportunity to extract a large amount of clinical information to improve the performance of prognostic models. The use of multiple artificial intelligence algorithms to select features with the highest mortality prediction values contributed to a significant increase in accuracy with an area under the ROC curve ≥90%, and the highest accuracy reaching an area under the ROC curve of 99.1-99.7% [8, 10, 19, 27, 34, 39, 40]. These methods are superior and more accurate than traditional scoring systems (SOFA, SAPS-II, SAPS III, APACHE-II, APACHE-III, APACHE-IV), which show moderate prediction accuracy (area under the ROC curve 0.73-0.96) [41-47].

AI techniques (*machine learning* and *deep learning*) have become valuable tools for supporting decision-making processes in healthcare, including diagnosis, monitoring, and predicting disease severity and mortality. These methods have demonstrated promising results across various medical applications, such as skin cancer classification, breast cancer detection, pneumonia classification, and predicting mortality from acute kidney injury [7, 14]. Emerging applications can provide higher prediction performance than classical statistical analysis by leveraging large-scale complex electronic health records and identifying the most reliable parameters, going beyond traditional statistical modeling. They can quickly evaluate large and complex databases with numerous variables to determine clinically significant risk levels for prognostic outcomes through intensive computational statistical modeling. In addition, machine and deep learning algorithms can identify hidden trends and unknown interactions between different variables that affect the outcome [18, 19, 27, 33, 34, 48].

AI techniques are increasingly being used to predict the outcomes of COVID-19 patients. In particular, the use of these algorithms to predict COVID-19 mortality is rapidly developing, which can quickly and effectively support clinical decision-making for COVID-19 patients at imminent risk of death [8, 10, 18, 36, 39, 48, 49].

AI applications, especially *machine learning* and *deep learning* algorithms, have great potential to support healthcare workers and professionals in decision-making, predicting complications and mortality rates in hospitalized patients. Medical validation should be performed by clinical experts, and these models can be implemented in various hospitals and healthcare settings [17].

However, despite the availability of several machine learning algorithms for predicting mortality in COVID-19 patients, their practical use is limited by factors such as the heterogeneity of patients' clinical profiles and risk factors, small sample sizes, and the lack of external validation of the prediction tools, which may reduce their applicability [14-16].

According to a review of multiple studies, the strongest predictors of mortality in COVID-19 patients, repeatedly reported, include advanced age, male gender, comorbidities (such as cardiovascular diseases, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, neurological disorders, chronic kidney disease, and cancer), low levels of calcium, albumin, red blood cells, and oxygen saturation, lymphocytopenia, and increased levels of blood urea nitrogen, creatinine, lactate dehydrogenase, C-reactive protein, D-dimers, respiratory rate, neutrophil count, interleukin-6, procalcitonin, bilirubin, ferritin, aspartate aminotransferase, and troponin [8, 18, 36].

In general, studies have highlighted the effectiveness of various *machine learning* models in predicting outcomes for COVID-19 patients, showing promising results in forecasting mortality and disease severity [8].

According to a study involving 235 hospitalized COVID-19 patients, the most important variables for predictive performance, in descending order, were lymphocytes, leukocytes, eosinophils, basophils, and hemoglobin. Among the six algorithms used, the SVM algorithm demonstrated the best predictive performance, with an ROC-AUC of 0.85, sensitivity of 0.68, specificity of 0.85, and an F1 score of 0.72. Thus, among patients with an estimated probability of 80-100% of having COVID-19, 82% were indeed infected, while only 12% of those with an estimated probability of 0-20% were diagnosed with the disease [21].

Aslam H. and Biswas S. predicted mortality in COVID-19 patients in real time using *machine learning* methods. The analysis evaluated well-known regression models (XGBoost, RF, and SVM) on datasets from the United States, India, Italy, and three continents - Asia, Europe, and North America. The dataset contained a total of 165,870 records, each with 67 parameters. The results demonstrated that these models are effective and can be used to predict mortality in COVID-19 patients [49].

Jamshidi E. et al. built a mortality prediction model based only on age, gender, and comorbidities (15 parameters) in 23,749 hospitalized and confirmed COVID-19 patients [25] according to the TRIPOD guidelines [50]. Six *machine learning* methods (LR, RF, ANN, k-NN, LDA, and NB) were evaluated. The RF mortality prediction algorithm had the highest efficiency: the area under the ROC curve was 0.79, sensitivity was 75%, and specificity was 70% [25].

The binary RF classifier, tested on 218 electronic medical records with 50 variables from ICU patients, achieved an accuracy of 80.28%, sensitivity of 81.82%, specificity of 79.43%, positive predictive value of 73.26%, negative predictive value of 84.85%, F1 score of 0.74, and an area under the ROC curve of 0.85. The reliable model for predicting ICU mortality identified lactate level as the most important factor, followed by temperature and the Glasgow Coma Scale [51].

A performance analysis of eight *machine learning* algorithms (J48, RF, k-NN, MLP, SVM, XGBoost, NB, and LR) for predicting mortality in COVID-19 patients used a dataset of 6,854 patients, including features such as CT severity score, demographics, risk factors, clinical symptoms, and lab results. The RF predictive model demonstrated the best results, with an accuracy of 97.2%, sensitivity of 100%, precision of 94.8%, specificity of 94.5%, F1 score of 97.3%, and an area under the ROC curve of 99.9%. This algorithm can quickly identify high-risk patients upon admission, potentially improving their survival chances. XGBoost, J48, k-NN, and MLP also showed good prognostic performance with ROC curve ≥93.9. Other *machine learning* algorithms (SVM, NB, and LR) also had acceptable performance, with the area under the ROC curve ranging from 81.2 to 88.9% [12].

Shi Y. et al. evaluated three *machine learning* algorithms (RF, PLS-DA, and SVM) for mortality prediction using a database of 4711 patients who were consecutively hospitalized in four hospitals. The analysis included only relatively accessible clinical parameters, including demographics, laboratory results, and clinical characteristics. The RF model, which evaluated 20 variables, showed the best performance with an area under the ROC curve of 0.859, with 5 significant predictors: mean arterial pressure, age, procalcitonin, blood urea nitrogen, and troponin. PLS-DA included 20 variables and had an area under the ROC curve of 0.775, with 5 significant predictors: procalcitonin, ferritin, C-reactive protein, D-dimers, and troponin. The SVM model analyzed 10 variables, with an area under the ROC curve of 0.828, and identified five key predictors: mean arterial pressure, age, aspartate aminotransferase, alanine aminotransferase, and C-reactive protein. Notably, nine variables (age, procalcitonin, ferritin, C-reactive protein, troponin, blood urea nitrogen, mean arterial pressure, aspartate aminotransferase, and alanine aminotransferase) were common to all three models and were identified as the most critical risk factors for COVID-19 mortality [14].

RF was the most effective machine learning algorithm (area under the ROC curve: 88%) for predicting mortality in COVID-19 patients. The algorithm identified key predictors of in-hospital mortality, including age, severity of respiratory injury (PaO2/FiO2), cardiac damage biomarkers (troponin and BNP), inflammatory markers (interleukin-6 and procalcitonin), creatinine, urea, albumin, and red blood cell distribution [48].

The RF mortality prediction algorithm can reliably forecast mortality at the time of admission for patients infected with SARS-CoV-2 in the ICU, with an area under the ROC curve of 83%, sensitivity of 70%, and a specificity of 75%. The most significant prognostic factors included gender, age, blood urea nitrogen, creatinine levels, international normalized ratio, albumin, white blood cell count, segmented neutrophil count, lymphocyte count, hemoglobin, and a history of neurological, cardiovascular, and respiratory disorders [37].

In a large-scale study, 7 *machine learning* algorithms were tested on a cohort of 263,007 patients with 41 clinical and demographic parameters. XGBoost showed the best results in predicting COVID-19-related mortality, with 96% accuracy, 95% precision, an F1 score of 95%, and an area under the ROC curve of 96%. Older age, pneumonia, diabetes, obesity, cardiovascular diseases, and kidney diseases were statistically significant factors associated with COVID-19 mortality [17].

According to another study comparing the effectiveness of 4 *machine learning* techniques (RF, XGBoost, SVM, and LR), the XGBoost algorithm, based on initial clinical data (demographics and comorbidities), produced the most accurate prediction models. Through systematic design-based optimization, this algorithm performed better in predictive modeling applications involving structured data [52].

Zhao S. et al. tested 4 *machine learning* algorithms (LR, RF, XGBoost, and ANN) on a cohort of 12,393 ICU patients. Routine variables used included age, gender, physiological parameters, and use of vasoactive drugs during the first 24 hours of hospitalization. Among the tested models, the XGBoost algorithm showed the highest performance in predicting the risk of mortality within 24 hours, achieving an area under the ROC curve of 0.97 [47].

Another study evaluated 4 *machine learning* methods (RF, LR, XGBoost, and SVM) on a database containing 4120 records with 38 variables for each hospitalized COVID-19 patient across 5 hospitals in Tehran, Iran. The XGBoost model showed higher performance compared to other models (accuracy 70%, sensitivity 77%, specificity 69%, and AUC 0.857). For RF, LR, and SVM models, the AUC was 0.836, 0.818, and 0.794, respectively [28].

A study comparing two mortality prediction algorithms in 2,348 hospitalized COVID-19 patients using clinical and radiological information found similar results for both the SVM (*machine learning*) and FNN (*deep learning*) algorithms. The area under the ROC curve was 0.803 and 0.864, sensitivity 0.816 and 0.814, specificity 0.791 and 0.759, and accuracy 0.813 and 0.766, respectively [26].

Booth A. et al. used the SVM *machine learning* algorithm to predict mortality in patients with SARS-CoV2 based solely on a set of serum biomarkers. Using five readily available laboratory parameters (C-reactive protein, blood urea nitrogen, serum calcium, serum albumin, and lactic acid) from 398 patients, the model achieved a sensitivity of 91%, a specificity of 91%, and an area under the ROC curve of 0.93 [35].

Ali M. et al. evaluated 7 *machine learning* algorithms for predicting mortality in a cohort of 696 hospitalized COVID-19 patients. The scientists highlighted that the k-NN classifier performed best in predicting mortality compared to other machine learning algorithms, achieving an accuracy of 95.25%, a sensitivity of 95.30%, a precision of 92.7%, a specificity of 93.30%, an F1 score of 93.98%, and an area under the ROC curve of 96.90%. Male gender, intensive care unit admission, and alcohol consumption were the three most important predictors of COVID-19 mortality [8].

Pourhomayoun and Shakibi assessed the effectiveness of six machine learning algorithms (SVM, ANN, RF, J48, LR, and k-NN) for predicting mortality rates in COVID-19 patients. The study included a dataset of more than 2,670,000 patients infected with laboratory-confirmed SARS-CoV-2 from 146 countries. The original dataset contained 32 items for each patient, including symptoms, comorbidities, demographics, and physiological data. ANN achieved the highest performance in predicting the mortality of COVID-19 patients with an accuracy of 89.98%. This result is nearly equivalent to the k-NN (89.83%) and SVM (89.02%) algorithms, but slightly higher than RF (87.93%), LR (87.91%), and J48 (86.87%) [36].

Another prognostic model based on the SIMPLS (*Statistically inspired modification of partial least square*) algorithm, performed on a group of 250 hospitalized patients with COVID-19, assessed 18 clinical parameters and comorbidities, as well as 3 blood biochemical markers. The most significant predictors of in-hospital mortality were coronary artery disease, diabetes mellitus, altered mental status, age over 65 years, and dementia. C-reactive protein, prothrombin, and lactate dehydrogenase were the most important biochemical predictors of in-hospital mortality [24].

Some scientists believe that using more variables can improve the performance of mortality prediction models for patients with COVID-19 [28].

Conclusions

1. Artificial intelligence techniques, such as *machine learning* and *deep learning*, offer potential advantages over traditional scoring assessments, making them a valuable tool to support decision-making in healthcare, including diagnosis, monitoring, and predicting disease severity and mortality.
2. Information generated by *machine learning* and *deep learning* algorithms, which involve easily accessible and interpretable data, can help healthcare profes-

sionals make the right decisions to provide appropriate and timely care to COVID-19 patients, improve patient outcomes, reduce the burden on health systems, and ultimately reduce mortality.
3. Strong predictors of mortality in COVID-19 patients that have been repeatedly reported include older age, male gender, comorbidities, decreased calcium, albumin, and red blood cells, low oxygen saturation, lymphocytopenia, increased blood urea nitrogen, creatinine, lactate dehydrogenase, C-reactive protein, D-dimers, respiratory rate, neutrophil count, interleukin-6, procalcitonin, bilirubin, ferritin, aspartate aminotransferase, and troponin.
4. Implementing artificial intelligence algorithms in each specific healthcare service will be crucial to improving prediction efficiency, enhancing the quality of healthcare services, reducing the burden on healthcare workers, lowering overall patient care costs, and increasing their applicability in clinical practice.

Competing interests

None declared.

Authors' contributions

Substantial contributions to the concept and design of the work VM, CT, IG, SS, OA. Substantial contributions to the acquisition of data VM, CT, IG. Substantial contributions to the analysis and interpretation of data VM, CT, RB, SS, SC, OA. Drafting the article VM, CT, IG, OA. Critically reviewing the article for important intellectual content RB, SS, SC, OA. Final approval of the version to be published VM, CT, IG, RB, SS, SC, OA. Taking responsibility and being accountable for all aspects of the work VM, RB, SC, OA.

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