Machine learning techniques for mortality prediction in emergency departments: a systematic review

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INTRODUCTION

The improved life expectancy in Europe and most developed countries has increased admissions to the emergency departments (EDs), especially for elderly people who have a higher risk of morbidity and mortality. Also, having more intercity and intracity travels and organised emergency medical services to transfer these patients to ED brought more importance as well as patient load to EDs. The average rate of mortality among in-patient admissions is around 2% in USA, indicating the necessity of using clinical deterioration prediction models. Moreover, a recent study has shown that some in-hospital deaths due to clinical deterioration can be avoided.

Vital signs including heart rate (HR), pulse rate (PR), respiratory rate (RR), oxygen saturation (SpO2), blood pressure (BP), body temperature (TP) and Glasgow coma scale (GCS) are essential parts of the patients' monitoring process. The data received from these parameters could be considered as the cheapest and the most important information, which could easily be collected during admission. Although vital signs are among the first data that clinicians observed to have an initial assessment about the patients' condition and have been used in clinical practice for over a century, few studies have effectively quantified their performance in various clinical applications. In recent years, various studies have emphasised that changes in vital signs happen several hours before a serious adverse event. Nowadays, vital signs play a key role in identification of patients with...
risk of deterioration in ED, however deterioration often occurs unnoticed or is not identified until it becomes too late to intervene.9

Machine learning (ML) addresses the question of how to build a computer model that automatically enhances performance through experiments, lying at the intersection of computer science, statistics and a variety of other disciplines concerned about automatic improvement over time, and inferring and decision-making under uncertainty.14 Various ML algorithms have been developed to solve a wide variety of problems. The most commonly used ML algorithms are supervised learning algorithms focusing on relationships and dependencies between the input and output features.15 Hence, we can identify the output values for unseen data based on the relationships learnt from the training data sets. Unsupervised learning is subset of ML that is used in pattern recognition and descriptive modelling without the use of output categories or data labelling.16

Because of enormous advancements in the development of modern ML algorithms such as deep learning, the availability of large databases and increased computational power, ML has progressed rapidly over the last two decades from laboratory curiosity to practical technology in a wide range of commercial applications. Consequently, utilisation of ML techniques in the healthcare domain is increasing rapidly, and the list of tasks where ML has matched or outperformed physicians is growing. Clinical outcome prediction is one challenge receiving attention, and by improvement of ML techniques, the ML-based systems aim to outperform conventional clinical scoring systems.14 17

Various studies have been made in this area evaluating the prediction accuracy of in-hospital mortality, cardiac arrest and intensive care unit transfer. To reach this goal, various techniques such as logistic regression (LR), support vector machine (SVM), K-nearest neighbours (KNN), decision tree (DT), random forest (RF), Gaussian process (GP) and artificial neural networks (NN) have been applied, and the results confirmed the appropriateness of using ML in this area.14 The capability of handling large data sets is the most considerable advantage of ML algorithms, which can result in more accurate prediction of clinical outcomes. Currently, we have various prediction models, using different techniques, in order to improve the triage process and to provide better identification of high-risk patients.18 19 Although several studies based on different models were conducted, no single model has yet proved to be superior regarding clinical efficacy.20–24

Despite the use of vital signs in patient monitoring and clinical decision-making, the importance of specific types of vital signs, their correlation and frequency of registration to best prevent adverse events and in-hospital mortality is still unclear.9 However, ML could be a good solution for these challenges. Considering the possible role of ML models in prediction of clinical deterioration of patients in EDs,25 it is essential to analyse and merge the results of previous studies to have an updated overview of the state-of-the-art. This systematic review focused on the clinical efficacy and technical implications of ML-based models in prediction of mortality using vital signs predictors in patients admitted to EDs.

MATERIALS AND METHODS
This systematic review was conducted in the period from July 2020 to August 2021. The main questions addressed by this study are presented in table 1.

Search strategy and study selection
Three databases including Medline (PubMed), Scopus and Embase (Ovid) were targeted. Relevant articles were extracted using a broad range of relevant keywords. We stratified keywords into five groups namely, ML keywords, medical keywords, document type, publication year and language. The keywords in a group were paired using OR operators and all groups were paired using AND operators. Table 2 shows the search keywords that were applied to the titles, abstracts and full text in the three databases.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Research questions</th>
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</thead>
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<tr>
<td>Q1</td>
<td>What ML techniques have been used to predict in-hospital mortality in EDs?</td>
</tr>
<tr>
<td>Q2</td>
<td>What are the common vital signs variables used in studies?</td>
</tr>
<tr>
<td>Q3</td>
<td>How researchers prepared data for ML techniques?</td>
</tr>
<tr>
<td>Q4</td>
<td>What are the approaches to solve the problem (eg, binary classification or time series prediction)?</td>
</tr>
<tr>
<td>Q5</td>
<td>What are the challenges and open issues in this domain?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Search keywords in different groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 — ML keywords</td>
<td>Artificial intelligence, machine learning, deep learning, learning algorithms, supervised machine learning, unsupervised machine learning</td>
</tr>
<tr>
<td>Group 2 — Medical keywords</td>
<td>Clinical deterioration, mortality, in-hospital mortality, death, vital sign, emergency departments</td>
</tr>
<tr>
<td>Group 3 — Document type</td>
<td>Journal</td>
</tr>
<tr>
<td>Group 4 — Publication year</td>
<td>1 January 2010 to 1 August 2021</td>
</tr>
<tr>
<td>Group 5 — Language</td>
<td>English</td>
</tr>
<tr>
<td>Final result</td>
<td>(Group 1) AND (Group 2) AND (Group 3) AND (Group 4) AND (Group 5)</td>
</tr>
</tbody>
</table>

ML, machine learning.
Inclusion and exclusion criteria are listed in table 3. Our queries for three databases can be found in online supplemental file S1.

**Data extraction**

Three researchers (AN, MM and AE) screened the title and extracted abstracts, independently. The screening process was done using the Covidence tool. Then, two researchers (AN and TS) read the full texts, independently resolving the disagreement by supervision of the senior researcher (UKW). Spreadsheets for item extraction were prepared based on the critical appraisal and data extraction for systematic reviews of prediction modelling studies (CHARMS) checklist.\(^\text{26}\) The extracted items include study design, publication date, source of data, study population, outcomes, time horizon, considered vital signs predictors, data preprocessing, model development, model performance, model validation and evaluation, and the interpretation.

**Risk of bias assessment**

Risk of bias (ROB) for each study was assessed by using the prediction risk of bias assessment tool (PROBAST) checklist\(^\text{27}\) and reported based on an adapted form.\(^\text{28}\) Extracted articles were classified into three different categories (low, high and unclear). A study is considered as having a high ROB if the study has at least one high ROB in four domains. ROB assessment of each study was checked by two of our researchers (AN and MN-B); disagreements were resolved in collaboration with a senior researcher (UKW).

**Patient and public involvement**

No patient involved.

**RESULTS**

The initial search resulted in 7466 records, which after removing duplicates, evaluation of eligibility for inclusion, full-text assessment, quality assessment and review of the references of the included papers, was narrowed down to fifteen studies. The study selection flowchart is shown in figure 1.

General information, as well as study design and population of included studies, are summarised in table 4. Twelve out of 15 articles were published after 2019, which indicates an increased interest recently among researchers to explore the capability of ML in prediction of clinical outcomes in EDs.

**Studies design**

Among extracted articles, 14 studies have used electronic data of the related hospitals, while 1 of the studies was based on registry-based public data.\(^\text{29}\) One of the essential parts in utilising ML techniques in each application is gathering and preparation of the data set, which has a high impact on the performance of the final ML-based system. In general, ML techniques need an extensive data set to produce good results, and the performance of ML models depends largely on the number of training examples.\(^\text{14}\) Based on Riley et al.\(^\text{26}\) 13 studies had enough number of patients to build acceptable models through their data sets, while 2 studies proposed a model based on only 100 and 445 patients.\(^\text{31,32}\)

**Vital signs predictors**

We considered studies, which utilised vital signs among their predictors in building models. The vital signs set used in extracted articles included HR, PR, RR, SpO\(_2\), BP, TP and GCS (table 4). BP and TP were the most widely used vital sign predictors among the included studies. SpO\(_2\), RR and HR were common vital signs, which were used in 13, 13 and 11 articles, respectively, while GCS and PR were the least commonly used vital signs. Besides the vital signs, all studies used other clinical predictors such as demographic variables (eg, age, sex, race, marital status), medical history,18 19 22 29 31–40 arrival mode (walk-in and ambulance),18 29 32 36 blood tests (eg, albumin, creatinine, haemoglobin, potassium, sodium, white cell count, urea),21 33 35–37 39 ECG signal,31 chief complaints,18 19 29 34 36 38 40 length of stay at hospital,22 medications,19 32 36–38 comorbidities,36 diagnoses,22 38 medical history,18 36–38 and triage information.19 21 36 38

**Data preparation**

Real-world data sets often need to be transformed, cleaned or changed before use. These data sets may contain missing values, noise and even wrong entries or inconsistencies.\(^\text{41}\) Missing values issue is one of the main challenges in clinical data mining\(^\text{12}\) that often provide additional information about patients. Therefore, in almost all cases, raw data will need to be preprocessed before it can be used as the basis for ML modelling. This preprocessing may affect the final model, and the specific steps are important to clarify. However, 10 articles did not utilise proper techniques to impute missing values and excluded up to 92% of incomplete patients’

### Table 3 Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prediction of in-hospital mortality should be the main aim of the study</td>
<td>Studies which are conference articles, posters, abstracts, books or book chapters and review articles.</td>
</tr>
<tr>
<td>The study should be done at ED.</td>
<td>Studies which were done in paediatrics field.</td>
</tr>
<tr>
<td>The study should be done on adult patients.</td>
<td>Non-English studies.</td>
</tr>
<tr>
<td>ML algorithms should be used for the prediction task.</td>
<td></td>
</tr>
<tr>
<td>Vital signs variables should be among the predictors used to build ML models.</td>
<td></td>
</tr>
</tbody>
</table>

ED, emergency department; ML, machine learning.
records in some studies. Different approaches, including replacing missing values with median, considering missing values as a special value and imputation using GP technique were applied to impute missing values.

**Outcome and time horizon**

The percentage of target patients in the nine included studies is less than 6%. It should be noted that Liu et al. and Karlsson et al. have conducted their studies on small data sets containing 100 and 445 patients from which 40 and 63 patients died during hospitalisation, respectively. Since the outcome patients in most studies were few, large data sets should be collected to obtain enough event patients.

As the main aim of the included studies was building ML models to predict mortality at EDs, these articles should specify how much earlier their models can predict mortality. However, as shown in table 5, only six studies reported their time horizon for mortality prediction; 9–12 min, 2 hours, 24 hours, 72 hours, 7 days, 28 days, 30 days and 31 days ahead were reported as time horizons. Since studies in this area try to predict mortality in advance, all studies must report their time horizons, meaning the time that their models provide clinicians to intervene before mortality occurs.

**Imbalanced data**

Fourteen studies utilised classification approaches to predict mortality at EDs. Since the number of patients who died during hospitalisation for many studies is small, some proper preprocessing techniques such as balancing classes are needed. In addition, except, all other studies stratified patients into two groups, for example, non-survived patients and survived patients, but the number of patients who died during hospitalisation was much lower. This challenge, which is called imbalanced data, can affect the performance of ML models significantly; thus, proper techniques should be applied to address this challenge.
Nevertheless, only two studies\textsuperscript{22,33} mentioned this challenge and used Synthetic Minority Over-sampling Technique (SMOTE)\textsuperscript{43} to address it.

**Machine learning models**

As shown in table 5, eight ML techniques have been utilised in the included studies. RF was the most common ML technique and was used in nine studies. A brief description and list of advantages and disadvantages of each ML technique is summarised in table 6. Although most studies have been made during the last 5 years, we observed traditional algorithms such as LR more than advanced algorithms, applied to build predictive models in five studies.

**Validation and evaluation**

Ten articles used k-fold cross-validation,\textsuperscript{21,22,29,31,32,34,35,37–39} while one study applied bootstrapping technique for validation purpose.\textsuperscript{36} Two studies split their data into training and test sets and used a portion of the training set for validation.\textsuperscript{19,40} Three studies investigated the generalisation capability of their models using external validation, while the rest of the studies were internally validated. Researchers have used different metrics for evaluation of ML models in predicting mortality at EDs. The area under the curve (AUC) metric was used in 14 articles. Eight studies assessed the performance of ML models using sensitivity and specificity. Five studies presented the accuracy of models, while positive predictive value and negative predictive value were used in three studies. The Brier Score, positive likelihood ratio, negative likelihood ratio, and false positive rate were less common metrics used in two studies, one, one, and one study, respectively.

**Personalised model**

Patients’ characteristics should be considered in developing predictive models and the potential impact on the improvement of models’ performance should be investigated. However, among the included studies, only one study used information of each patient to predict the risk of mortality for the same patient.\textsuperscript{40} They considered patients’ vital sign trajectories as time series data and introduced an ML model to follow-up the trends of vital signs for each patient and by that they tried to consider patients’ characteristics, while the other studies only build one model for the whole population and categorised patients into two groups and binary classifiers using different ML algorithms were built.

<table>
<thead>
<tr>
<th>ID</th>
<th>Authors</th>
<th>Year</th>
<th>Country</th>
<th>Study type</th>
<th>Population</th>
<th>Outcome portion (%)</th>
<th>Patients type</th>
<th>Mean age (y)</th>
<th>Male (%)</th>
<th>Vital signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>Levin et al</td>
<td>2017</td>
<td>USA</td>
<td>Retrospective</td>
<td>172726</td>
<td>0.40</td>
<td>All admissions</td>
<td>46</td>
<td>44.7</td>
<td>TP, HR, RR, SBP, SpO\textsubscript{2}</td>
</tr>
<tr>
<td>A2</td>
<td>Klug et al</td>
<td>2020</td>
<td>Israel</td>
<td>Retrospective</td>
<td>799522</td>
<td>1.55</td>
<td>All admissions</td>
<td>55</td>
<td>51.5</td>
<td>TP, HR, SBP, DBP, SpO\textsubscript{2}</td>
</tr>
<tr>
<td>A3</td>
<td>Faisal et al</td>
<td>2020</td>
<td>UK</td>
<td>Retrospective</td>
<td>24696</td>
<td>5.33</td>
<td>All admissions</td>
<td>63</td>
<td>46.9</td>
<td>RR, SpO\textsubscript{2}, SBP, PR, GCS, TP</td>
</tr>
<tr>
<td>A4</td>
<td>Kwon et al</td>
<td>2020</td>
<td>South Korea</td>
<td>Retrospective</td>
<td>23587</td>
<td>3.98</td>
<td>Infectious patients</td>
<td>63</td>
<td>46.1</td>
<td>SBP, RR, TP, HR</td>
</tr>
<tr>
<td>A5</td>
<td>Raita et al</td>
<td>2019</td>
<td>USA</td>
<td>Retrospective</td>
<td>135470</td>
<td>2.10</td>
<td>All admissions</td>
<td>46</td>
<td>56.8</td>
<td>TP, PR, SBP, RR, SpO\textsubscript{2}</td>
</tr>
<tr>
<td>A6</td>
<td>Liu et al</td>
<td>2011</td>
<td>Singapore</td>
<td>Retrospective</td>
<td>100</td>
<td>40.00</td>
<td>All admissions</td>
<td>65</td>
<td>63</td>
<td>RR, PR, SBP, DBP, SpO\textsubscript{2}</td>
</tr>
<tr>
<td>A7</td>
<td>Karlsson et al</td>
<td>2021</td>
<td>Sweden</td>
<td>Retrospective</td>
<td>445</td>
<td>14.1</td>
<td>Infectious patients</td>
<td>73</td>
<td>52.6</td>
<td>HR, SBP, DBP, RR, SpO\textsubscript{2}</td>
</tr>
<tr>
<td>A8</td>
<td>Chen et al</td>
<td>2021</td>
<td>Taiwan</td>
<td>Retrospective</td>
<td>52626</td>
<td>9.4</td>
<td>Infectious patients</td>
<td>72</td>
<td>58.3</td>
<td>HR, SBP, DBP, TR, SpO\textsubscript{2}</td>
</tr>
<tr>
<td>A9</td>
<td>Joseph et al</td>
<td>2020</td>
<td>USA</td>
<td>Retrospective</td>
<td>445925</td>
<td>&lt;13</td>
<td>All admissions</td>
<td>53</td>
<td>45.9</td>
<td>HR, SBP, DBP, RR, SpO\textsubscript{2}</td>
</tr>
<tr>
<td>A10</td>
<td>Rodriguez et al</td>
<td>2021</td>
<td>Columbia</td>
<td>Retrospective/ prospective</td>
<td>2510</td>
<td>11.5</td>
<td>Infectious patients</td>
<td>62</td>
<td>49.8</td>
<td>SBP, DBP, TR, RR, SpO\textsubscript{2}</td>
</tr>
<tr>
<td>A11</td>
<td>Soffer et al</td>
<td>2020</td>
<td>Israel</td>
<td>Retrospective</td>
<td>118262</td>
<td>5.3</td>
<td>All admissions</td>
<td>73</td>
<td>52.6</td>
<td>HR, SBP, DBP, TR, RR, SpO\textsubscript{2}</td>
</tr>
<tr>
<td>A12</td>
<td>van Doorn et al</td>
<td>2021</td>
<td>Netherlands</td>
<td>Retrospective</td>
<td>1344</td>
<td>13</td>
<td>Infectious patients</td>
<td>71</td>
<td>54.4</td>
<td>HR, SBP, DBP, TR, RR, SpO\textsubscript{2}</td>
</tr>
<tr>
<td>A13</td>
<td>Taylor et al</td>
<td>2015</td>
<td>USA</td>
<td>Retrospective</td>
<td>5278</td>
<td>4.92</td>
<td>Infectious patients</td>
<td>65</td>
<td>55</td>
<td>HR, TR, SBP, DBP, RR, SpO\textsubscript{2}</td>
</tr>
<tr>
<td>A14</td>
<td>Perng et al</td>
<td>2019</td>
<td>Taiwan</td>
<td>Retrospective</td>
<td>42220</td>
<td>4.71</td>
<td>Infectious patients</td>
<td>64</td>
<td>56.5</td>
<td>SBP, GCS, TP, HR</td>
</tr>
<tr>
<td>A15</td>
<td>Shamout et al</td>
<td>2020</td>
<td>UK</td>
<td>Retrospective</td>
<td>37284</td>
<td>0.80</td>
<td>All admissions</td>
<td>68</td>
<td>48.8</td>
<td>HR, SBP, RR, TR, SpO\textsubscript{2}</td>
</tr>
</tbody>
</table>

DBP, diastolic blood pressure; GCS, Glasgow coma scale; HR, heart rate; PR, pulse rate; RR, respiratory rate; SBP, systolic blood pressure; SpO\textsubscript{2}, oxygen saturation; TP, body temperature.
Risk of bias assessment

There is a significant amount of incomplete reporting within the studies’ results. For instance, most studies did not report information about the tuning process of ML models and hyperparameter values considered during the model training process. A summary of the PROBAST assessment is shown in table 7. As shown, participants’ selection was done properly except in two studies. However, most studies had a high ROB in the statistical analysis domain. Among the studies, only Joseph et al utilised transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guideline and provide adequate information about feeding data to models and architecture of implemented NN, so only this study was considered as low ROB in the statistical domain.

DISCUSSION

Weaknesses and strengths of included studies

This review consisted of 15 studies that developed ML-based models to predict mortality in EDs. Our analysis showed that most studies described the data sets in sufficient detail and had enough number of participants. Moreover, the outcome domain had the lowest ROB which shows most studies had a clear outcome definition. However, we found several methodological and reporting shortcomings, and this can lead to poorer performance than reported when the models are deployed in real life. Many studies skipped or failed to report important phases such as data preprocessing, handling missing values and model development. It has been stated that up to 80% of data analysis is spent on data cleaning and
various researchers still have applied traditional in ML and introducing novel and effective models. Moreover, despite the dramatic advances of ML predictive models in clinical environments, some researchers have discussed the poor effectiveness and generalisation power and avoiding overfitting, needed to be tuned to gain the best performance used in the studies. Most ML models have parameters that needed to be tuned to gain the best performance and generalisation power and avoiding overfitting, but most studies did not provide information about the models’ validation process and finding the hyper-parameters of the models. Of 15 studies, 14 studies

<table>
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<tr>
<th>Algorithm</th>
<th>Description</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR⁵⁸</td>
<td>LR is a supervised ML algorithm adopted from linear regression. It can be used for classification problems and finding the probability of an event happening.</td>
<td>Fast training, good for small data sets, easy to understand.</td>
<td>Not very accurate, not proper for non-linear problems, high chance of overfitting, not flexible to adopt to complex data sets.</td>
</tr>
<tr>
<td>DT⁵⁹</td>
<td>DT is a supervised ML algorithm that solves a problem by transforming the data into a tree representation where each internal node represents an attribute, and each leaf denotes a class label.</td>
<td>Easy to understand and interpret, robust to outliers, no standardisation or normalisation required, useful for regression and classification.</td>
<td>High chance of overfitting, not suitable for large data sets, adding new samples lead to regeneration of the whole tree.</td>
</tr>
<tr>
<td>KNN⁶⁰</td>
<td>KNN is a supervised and instance-based ML algorithm. It can be used when we want to forecast a label of a new sample based on similar samples with known labels. Different similarity or distance measures such as Euclidean can be used.</td>
<td>Simple and easy to understand, easy to implement, no need for training, useful for regression and classification.</td>
<td>Memory intensive, costly, slow performance, all training data might be involved in decision-making.</td>
</tr>
<tr>
<td>SVM⁶¹</td>
<td>SVM is an instance-based and supervised ML technique that generates a boundary between classes known as hyperplane. Maximising the margin between classes is the main goal of this technique.</td>
<td>Efficient in high dimensional spaces. Effective when the number of dimensions is greater than the number of samples, long training time, useful for regression and classification.</td>
<td>Not suitable for large data sets, not suitable for noisy data sets, Regularisation capabilities which prevent overfitting, handling non-linear data.</td>
</tr>
<tr>
<td>GB⁶²</td>
<td>GB is a supervised ML algorithm, which produces a model in the form of an ensemble of weak prediction models, usually DT. GB is an iterative gradient technique that minimises a loss function by iteratively selecting a function that points towards the negative gradient.</td>
<td>High accuracy, high flexibility, fast execution, useful for regression and classification, robust to missing values and overfitting.</td>
<td>Sensitive to outliers, not suitable for small data sets, many parameters to optimise.</td>
</tr>
<tr>
<td>RF⁶³</td>
<td>RF is an ensemble and supervised ML algorithm that is based on the bagging technique, which means that many subsets of data are randomly selected with replacement and each model such as DT is trained using one subset. The output is the average of all predictions of various single models.</td>
<td>High accuracy, fast execution, useful for regression and classification, robust to missing values and overfitting.</td>
<td>Not suitable for limited data sets, may change considerably by a small change in the data.</td>
</tr>
<tr>
<td>NN⁶⁴</td>
<td>NN is a family of supervised ML algorithms. It is inspired by biological neural network of the human brain. NN consists of input, hidden, output layers and multiple neurons (nodes) carry data from input layer to output layer.</td>
<td>Accurate, suitable for complex, non-linear classification and regression problems.</td>
<td>Very slow to train and test, requires large amount of data, computationally expensive and prone to overfitting.</td>
</tr>
<tr>
<td>DNN⁶⁵</td>
<td>DNN is a family of supervised ML algorithms. DNN is based on NN where the adjective ‘deep’ comes from the use of multiple layers in the network. Usually having two or more hidden layers counts as DNN. There are some specific training algorithms and architecture such as LSTM, GAN, CNN for DNNs. DNNs provide the opportunity to solve complex problems when the data are very diverse, unstructured and interconnected.</td>
<td>High accuracy, features are automatically deduced and optimally tuned, robust to noise, architecture is flexible.</td>
<td>Needs very large amount of data, computationally expensive, not easy to understand, no standard theory in selecting the right settings, difficult for less skilled researchers.</td>
</tr>
</tbody>
</table>

CNN, convolutional neural networks; DNN, deep neural networks; DT, decision tree; GAN, generative adversarial networks; GB, gradient boosting; KNN, K-nearest neighbours; LR, logistic regression; LSTM, long-short term memory networks; ML, machine learning; NN, neural networks; RF, random forest; SVM, support vector machine.

data preparation, so these phases are very crucial for having an ML predictive model with good performance. It also could be one of the reasons why some researchers have discussed the poor effectiveness of ML predictive models in clinical environments. Moreover, despite the dramatic advances in ML and introducing novel and effective models, various researchers still have applied traditional ML techniques such as LR and DT. For instance, we found that LR is the third most common algorithm used in the studies. Most ML models have parameters that needed to be tuned to gain the best performance and generalisation power and avoiding overfitting, but most studies did not provide information about the models’ validation process and finding the hyperparameters of the models. Of 15 studies, 14 studies
are retrospective studies and only three studies have evaluated their models based on external validation. The ultimate aim of included studies was to predict mortality in EDs ahead of time to provide enough time for clinicians to intervene and prevent mortality. However, only six studies have provided their time horizon, the time that clinicians have to treat the patients. The other studies have built binary classification algorithms to stratify patients into two classes, and their models do not have the capability to be used in practice.

**Clinical considerations and prospective**

A recent systematic review on the value of vital sign trends in monitoring and predicting clinical deterioration showed a lack of research and knowledge regarding the importance of vital signs in clinical deterioration of ED patients. Even though considering the vital sign as cheap and available clinical predictors, there is a hypothesis stating the lack of evidence to support the usefulness of continuous monitoring of vital signs as a daily routine of clinical practice. The other barrier refers to the comparison between ML methods and conventional LR for clinical prediction models. A recent systematic review showed no performance benefits of ML methods over LR. However, as mentioned in the previous section, this conclusion could be due to lack of enough attention to the important stages and practical issues such as data preparation or models’ tuning, and consequently results are not satisfactory and implemented models are not robust. Therefore, further studies need to be performed to prove the superiority of ML algorithms over conventional models. It seems that there is still a long way to go for having ML algorithms as the choice of clinical deterioration in EDs. The increase of studies in this field during the last few years proves an increased attention to appraise the capabilities of ML methods in clinical practice.

**Challenges and recommendations for future work**

Perhaps in this research area, the main challenge is integration of ML models into clinical practice. A recent systematic review based on performance metrics, particularly AUC, showed that ML predictive models outperformed usual care in most detection and prediction tasks at ED. However, the authors mentioned that many studies have limited applicability to clinical practice and there are other considerations more than performance metrics as well as barriers that should be taken into account to have successful ML models in real life. Therefore, despite the great research successes in building ML-based predictive models for clinical practice, there remain few examples of ML models being successfully integrated into the daily routine or critical parts of clinical environments. This reveals that what is being done in research is not completely in line with the realities of clinical practice. In this section, we mention some of these issues and technical barriers, then present recommendations on how to address the most prominent issues and encourage researchers to take them into account.

Our analysis indicated that most studies are retrospective. However, the impact of ML techniques in clinical environment will need further validation in randomised...
control trials and prospective studies before widespread clinical adoption where the data could be incomplete and noisy with high level of uncertainty. **Recommendation 1:** we recommend that besides building models using historical collected data, researchers consider prospective analysis and think about building adaptive models that can monitor patients in real-time.

Although external validation is one of the most rigorous ways to assess the generalisation power of predictive models, it is still one of the common approaches for showing the robustness of predictive models.** Recommendation 2:** we recommend that researchers investigate the performance of their models using external validation to have a better estimation of the generalisation power of their models. **Recommendation 3:** regarding the preprocessing phase, since some steps such as data cleaning, handling missing and noisy values are an inevitable part of each data analysis study, we recommend that researchers instead of ignoring records with missing values, use proper techniques to handle noisy and incomplete records. For instance, we recommend that complete case analysis is avoided and proper imputation techniques such as iterative multivariate imputation technique, which is one of the best approaches for imputing missing values is used instead. Another challenge in most studies is that the number of event patients is too low compared with non-event patients. This can lead to bias and overfitting during developing ML models, so proper under/over-sampling techniques such as SMOTE and its variations should be utilised to make a balance between classes before developing models.

Another issue is time horizon for prediction. Gerry et al recommended that time horizon should be limited to a few days at most, since signs of deterioration will probably not be observed for more than a few days.** Recommendation 4:** we suggest that researchers in this area choose a realistic time horizon rather than prediction of mortality after 6 or 12 months. Moreover, most of the included studies are based on building a single model for the whole population. **Recommendation 5:** as patients have different characteristics and norms, we recommend that patients’ characteristics, vital signs trajectories, trends, etc, are used for each individual patient to tune ML models to have a better performance in practice. **Recommendation 6:** we recommend that researchers find a way to make their results and workflow understandable and interpretable by humans. For instance, deep learning is one of the hottest research topics today, and it has been applied in different applications of clinical practice, but it has inherent limitations. For example, despite impressive results, it is not indicative of high-level reasoning and rationality. Such methods are often considered as a ‘black box’, where the decision logic is presented in millions of numerical weights and biases. This lack of transparency could have some legal and ethical implications and might increase distrust of ML models by patients and clinicians, and it might be one of the reasons that patients are likely to trust a clinician more than a machine. This has been described as a crucial problem for ML acceptance in clinical practice and attempts are underway to create more human interpretable models. For example, with the help of image-processing techniques, it is possible now to visualise the input and output of ML models; this makes the understanding of ML models easier.

Lack of widely accepted and utilised reporting or publication guidelines for implementing ML in clinical practice is a challenge that brings difficulty to the research quality assessment, especially for clinicians without a strong mathematics and computer science background. Another challenge for ML models is that they need a huge amount of labelled data to be trained, and the performance of ML models often depends on the performance of the human labelling the data. **Recommendation 7:** as this area is interdisciplinary in nature, it is imperative that clinicians and artificial intelligence experts become better at interdisciplinary collaboration to become more familiar with the needs, limitations and challenges in clinical and technical domains, which ultimately increases the quality of the predictive models. **Recommendation 8:** we recommend that researchers should be careful and accurate when reporting their studies. It has been shown that the quality of reporting of predictive models in this clinical domain is poor. Only with full and transparent reporting of information about all aspects of a predictive model, the ROB and the usefulness of that model can be assessed. It is recommended that researchers use available checklists such as Standard Protocol Items: Recommendations for Interventional Trials-Artificial Intelligence (SPIRIT-AI) for designing the trial, and TRIPOD and Consolidated Standards of Reporting Trials - Artificial Intelligence (CONSORT-AI) for reporting the findings to make sure that they provide sufficient information to clearly and accurately report their studies.

**Strengths and limitations of this study**

To the best of our knowledge, this study is the most recent systematic review on the topic of using ML algorithms to predict mortality at EDs. This study was done with the help of an experienced artificial intelligence expert, an experienced research librarian who is familiar with the health research area, and three expert clinicians at ED. Moreover, ROB analysis was done using PROBAST checkbox which has four domains that assess different aspects of studies. Data extraction was done using a standard checklist called CHARMS. However, our study has some limitations. First, it was not possible to quantify the analysis or a conduct meta-analysis due to the high heterogeneity of included studies. Also, we have considered the vital signs due to high availability at ED, while the role of other clinical predictors in patients’ clinical conditions should be investigated.
CONCLUSION
The application of ML methods to identify clinical deterioration remains equally challenging as identification of deterioration using track and trigger protocols and similar human-driven protocols. However, since the ML approaches are as diverse as the problem they deal with, assessment of various methods and their performance are needed. This systematic review was performed on the topic of utilisation of ML techniques to predict mortality at EDs using vital signs. Our systematic review of the literature provides an updated overview of the state-of-the-art on this topic (covering 2010 to 2021). Initially, 7466 potential articles were identified of which 15 were included in the analysis. After a comprehensive review of these 15 articles, we generated eight recommendations to increase the feasibility of implementing ML models in EDs. These recommendations provide actionable suggestions to be used to increase the quality of future work in this area.

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Contributors
All authors were involved in conception and design of the study. Literature search was conducted by AN under supervision of an expert librarian. AN, TS, MM and AE participated in screening and extracting relevant studies. AN, MM-B, TS and UKW were responsible for analysing, and drafting the manuscript. All authors made critical revisions. All authors approved the final manuscript. The corresponding author (AN) takes responsibility for the study as a whole.

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Supplemental material
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