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Review Article

Acute respiratory distress syndrome prediction using machine learning techniques: a systematic review and Meta-Analysis

Yang Fei[1*], Jian Hu[2] and Wei-qin Li[3]

[1]*JiangSu Health Commission, Nanjing, China*
[2]*School of mechanical engineering, Nanjing University of Science and Technology, Nanjing, China*
[3]*Surgical Intensive Care Unit (SICU), Eastern Theater General Hospital, Nanjing, China*

[*]**Corresponding author:** Yang Fei, JiangSu Health Commission, Nanjing, Chinak, Tel: +86-25-83620802, Fax: +86-25-83620802, E-mail: fei_yanggood@163.com

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Abstract

Objective: To systematically determine the predictive value of machine learning (ML) in the assessment of acute respiratory distress syndrome(ARDS).

Methods: Relevant studies were identified by searching the database up to November 2020. Patient clinical characteristics and diagnostic sensitivity and specificity were extracted. The summary receiver operating characteristic (ROC) curve was used to evaluate the accuracy of ML. A meta-analysis was performed to evaluate the clinical utility in the diagnosis and evaluation of ARDS.

Results: From 69 citations, ten were included in the meta-analysis, with a total of 21012 cases. We detected the heterogeneity of the studies and evidence of publication bias. The methodological quality was moderate. The pooled weighted sensitivity with a corresponding 95% confidence interval (CI) was 0.81 (95%CI: 0.78, 0.86), the specificity was 0.86 (95%CI: 0.83, 0.92), the positive likelihood ratio was 9.26 (95%CI: 7.30, 13.39), the negative likelihood ratio was 0.15 (95%CI: 0.06, 0.17), and the diagnostic odds ratio was 131.04 (95%CI: 79.48, 187.25). The area under the ROC curve was 0.877 (95%CI: 0.847, 0.923).

Conclusions: ML is a reliable, non-invasive modality with a high sensitivity and specificity for the assessment of ARDS. Nonetheless, it should be applied cautiously, and large-scale, well-designed trials are necessary to assess its clinical value.

Keywords: Machine Learning; Acute Respiratory Distress Syndrome; Meta-Analysis

Introduction

The acute respiratory distress syndrome (ARDS) is associated with severe respiratory failure in the presence of diffuse inflammation, increased pulmonary vasculature permeability, and loss of lung tissue aeration[1,2]. More recently, the focus has shifted from the treatment of ARDS to early identification and prevention of ARDS. Thus, it is important to recognize the ARDS risk factors early and eventually prevent its development. Some studies have shown that certain interventions could reduce the incidence of ARDS [3-5]. However, the patients enrolled in these trials had various risk factors, which made it difficult to predict ARDS in clinical practice [6]. Therefore, a prediction system for ARDS is needed to anticipate which patients are likely to develop ARDS.

Machine learning (ML) methods are used as a powerful tool for inspecting complicated relationships [7,8]. Since the early 1950s these methods have been used in medical science and played an impartible role in the area[9]. The focus of ML is typically the development of algorithms that mathematically optimize the outcome without specific instructions. ML algorithms function by first exposing a computer to a training data-set[10,11]. By means of various ML algorithms, the machine is trained to perform the required task. Its ability is then tested via a new set of data, the validation set. As the machine is exposed to more data, its ability to perform the required task becomes more refined[12]. Nowadays, more and more studies are focusing on the use of ML algorithms in the diagnosis or evaluation of ARDS and our meta-analysis provides summaries of the results of relevant studies, estimates of the average diagnostic accuracy of ML techniques, the uncertainty of this average, and the variability of the study findings around the estimates.

Material and method

Literature Search

PubMed, Embase, Elsevier ScienceDirect, Google Scholar, Scopus, Web of Science, Cochrane Register of Diagnostic Test Accuracy Studies and CNKI (China National Knowledge Infrastructure) database were performed to identify all the eligible papers. The search terms were used as the following: "acute respiratory distress syndrome (ARDS)" or "acute lung injury(ALI)", "machine learning" or "machine learning algorithms" or"deep learning" or "artificial intelligence" or "artificial neural networks". The publication languages were restricted to English and Chinese. Moreover, potentially relevant studies were evaluated by reviewing the titles and abstracts, and studies matching the criteria were carefully retrieved. If more than one study was published using the same data, only the study with a larger population was included. The literature search was updated on November, 2020. This systematic review was planned, conducted, and reported in adherence to the standards of quality for reporting meta-analysis.

Inclusion and exclusion criteria

Studies were included in the meta-analysis if they met all of the following criteria: 1) human study; 2) full text original article; 3) provided an outcome of the machine learning algorithms and ARDS patients prediction; 4) inclusion of at least 20 patients; 5) included an accepted reference method, all patients met the diagnostic criteria of ARDS; 6) provided explicit overview of data-set used in the study and origin of data source, 7) published in English or Chinese. Exclusion criteria were 1) no evaluation of the value of ML for the diagnosis of ARDS; 2) samples less than 20 patients; 3) review article (including meta-analyses), corresponding letter or editorial not reporting original data; 4) published in abstract form only; 5) published more than once; 6) Information regarding sensitivity and specificity weren't provided; 7) machine learning models and predictor variables used in the ARDS prediction weren't described clearly.

Quality assessment of studies

The methodological quality of the included studies was assessed independently by two observers using the revised tool for Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) instrument, a quality assessment tool specifically developed for systematic reviews of diagnostic accuracy studies[13]. The full QUADAS-2 tool consists of four domains: patient selection, index test, reference standard, and flow and timing. Each doymain was assessed in terms of the risk of bias according to the signaling questions, and the first three domains were judged in terms of concerns regarding applicability. Each question was scored "yes" if reported, "no" if not reported, or "unclear" if there was inadequate information in the article to make a judgment. To resolve disagreement between the two reviewers, a third reviewer assessed all of the involved items. The majority opinion was used for the analysis.

Data extraction

Three researchers extracted data from each study by using a structured sheet and entered the data into a dataybase. The following data were extracted from each study: the first author's last name, publication year, source journal, research design, study duration, retention and drop-out rate, surgical methods, patient's sex and age, sample size. For each study, values for true-positive (TP), false-positive, true-negative (TN), false-negative, sensitivity (Sen), specificity (Spe), positive likelihood ratio (PLR) and negative likelihood ratio (NLR) results for the detection of patients were extracted too, and 2×2 contingency tables were constructed.

Risk of bias assessment

Assessment of methodological quality was performed using the risk of bias assessment tool by the Cochrane Collaboration indicating the following bias domains: selection bias (random sequence generation, allocation concealment), performance/ detection bias (blinding of participants and personnel/blinding of outcome assessment), attrition bias (incomplete data outcome), reporting bias (selective reporting), and other bias. In addition, a bivariate box plot with Egger testing was used to assess the distributional properties of sensitivity versus specificity and for identifying possible outliers. After omitting these outliers and according to the results of the subgroups analysis, sensitivity analysis was performed and the change in heterogeneity was observed.

Statistical Analysis

The Q statistic of the Chi-square value test and the inconsistency index (I-squared, I^2) were used to estimate the heterogeneity of the individual studies using the STATA software 11.0 (Stata Corporation, Texas, USA). I^2 values were interpreted according to the proposal of Higgins, *et al.* [14], with heterogeneity determined as either low ($I^2 \leq 25\%$), medium ($25\% < I^2 \leq 50\%$) or high ($50\% < I^2 \leq 75\%$). In this study, meta-regression was used to explore such heterogeneity by relating the accuracy measurement to study level covariates.

If notable heterogeneities were detected, the test performance was summarized by using a random-effects coefficient binary regression model; otherwise, a fixedeffect coefficient binary regression model was used [15].

In test accuracy studies, one of the primary causes of heterogeneity is the threshold effect, and it arises when different cut-offs or thresholds are used in different studies to define a positive (or negative) test result. The Spearman correlation coefficient between the logit of sensitivity and the logit of (1-specificity) was computed to assess the threshold effect using Review Manager

5.0 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). A strong positive correlation would suggest a threshold effect, P<0.05 [16]. We constructed hierarchical summary receiver operating characteristic (ROC) curves to assess Sen and Spe [17]. The areas under the ROC curves (AUC) were used to analyze the diagnostic precision of ML for the prediction of ARDS.

Apart from variations due to the threshold effect, there are several other factors that can result in variations inaccuracy estimates amongst different test accuracy studies in a review. The presence of publication bias was visually assessed by producing a Deeks funnel plot and an asymmetry test with the STATA software. Publication bias was considered to be present if there was a nonzero slope coefficient (P<0.05) [18].

Results

From sixty-nine clinical studies, ten studies fulfilled the inclusion criteria and were included in the meta-analysis [19-28]. There were a total of 21012 ARDS cases. The search process and Study selection base on PRISMA flow chart in this systematic review has been outlined in figure 1. The characteristics of the ten clinical studies which were all retrospective studies are shown in table 1. All the authors used various types of ML including artificial neural networks (ANNs), genetic algorithm (GA)+ANNs, extreme gradient boosted decision tree (XGBoost), support vector machine (SVM), random forest (RF) ,natural language processing (NLP), deep learning (DL) and classification and regression tree (CART). The mean age of patients ranged from 52.6 years to 66.0 years with the proportion of males ranging from 55.3% to 71.9% (Table 1). The bivariate boxplot showed that no study was heterogeneous with respect to the other studies.

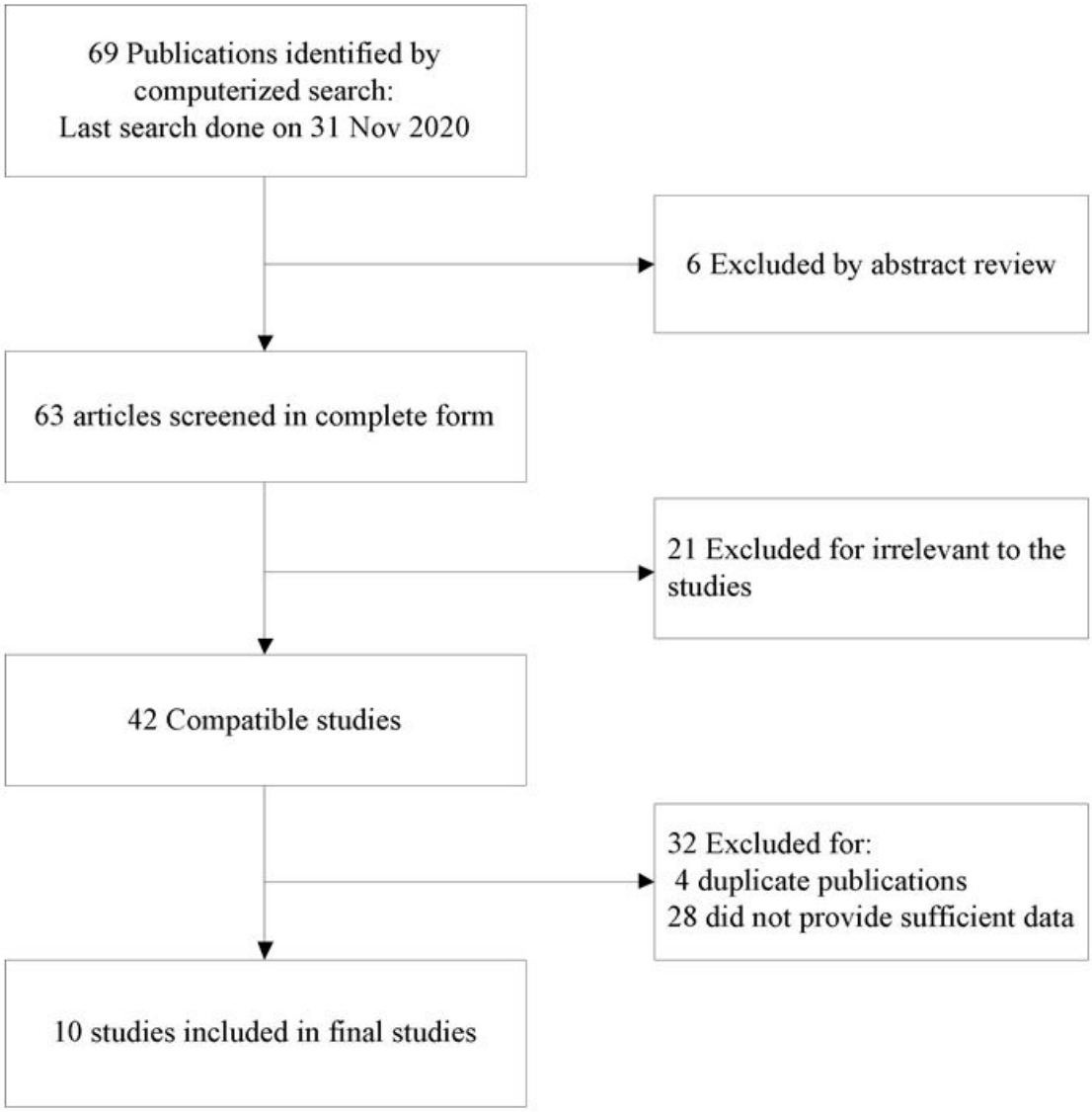

Figure 1: Systematic search and selection strategy

Author Year	Patients	Male%	Age (year)	Methods	modality	Sen	Spe
Chen YF 2014	723	61.9%	67.2+7.4	ANNs	35.9%	0.783	0.726
Damluji A 2011	508	58.3%	52.6+4.8	ANNs	46.3%	0.785	0.823
Zhang ZH 2015	1071	62.3%	55.7+8.2	ANNs	25.9%	0.800	0.731
Zeiberg D 2019	2743	57.3%	62.4+3.0	+GA	5.6%	0.556	0.859
Ding XF 2019	296	71.9%	65.4+18.1	XGBoost	30.7%	0.736	0.649
Reamaroon N 2019	401	64.5%	66.0+8.5	random forest	27.6%	0.873	0.769
Che Z 2016	398	56.9%	58.3+7.5	SVM	19.3%	0.720	0.762
Ahmed A 2014	3005	64.2%	63.7+10.6	deep learning	28.5%	0.815	0.945
Schmickl CN 2014	1948	70.2%	56.0+12.4	NLP CART	32.6%	0.839	0.897
Le S 2020	9919	55.3%	57.3+6.6	XGBoost	26.2%	0.806	0.823

ANNs: artificial neural networks GA:genetic algorithm
XGBoost: extreme gradient boosted decision tree SVM: support vector machine
NLP: natural language processing
CART: classification and regression tree
Table 1: Characteristics of the eleven clinical studies

As significant heterogeneity was found in the pooled analysis (I2=50.5%, P=0.038), summary Sen, Spe, PLR, and NLR were pooled by using a random effects coefficient binary regression model. The pooled weighted values were determined to be Sen: 0.81 (95%CI: 0.78, 0.86), Spe 0.86 (95%CI: 0.83, 0.92), PLR 9.26 (95%CI: 7.30, 13.39), NLR 0.15 (95%CI: 0.06, 0.17), and the diagnostic odds ratio (DOR) 131.04 (95%CI: 79.48, 187.25). Overall, mixed methods of ML had excellent Sen, Spe (Figure 2). The forest plots from ten studies on a per-patient basis are shown in figure 2. ROC curves are shown in figure 3. The AUC was 0.877 (95%CI: 0.847, 0.923).

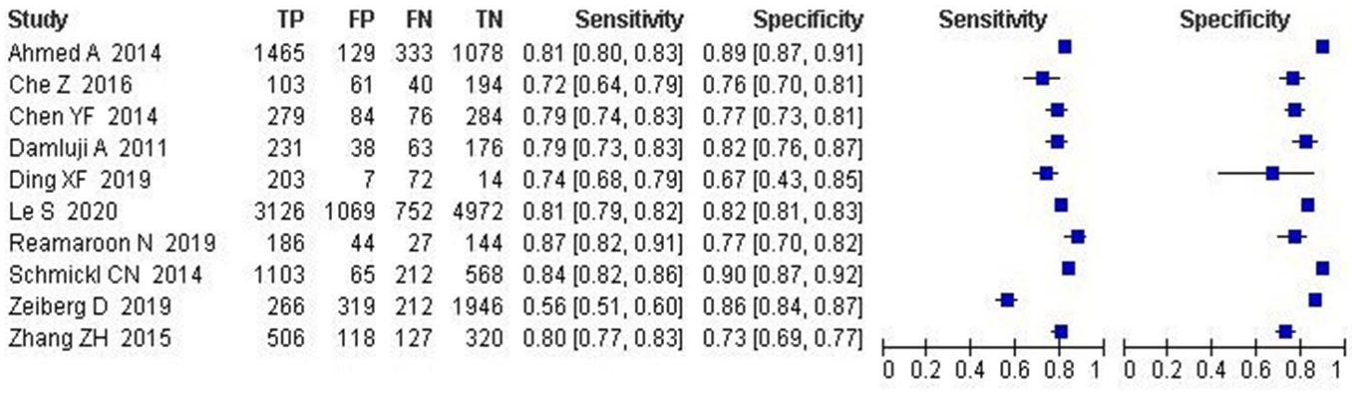

Figure 2: Forest plots of the Sensitivity, and Specificitywith corresponding 95%CIs of machine learning for the prediction of acute respiratory distress syndrome

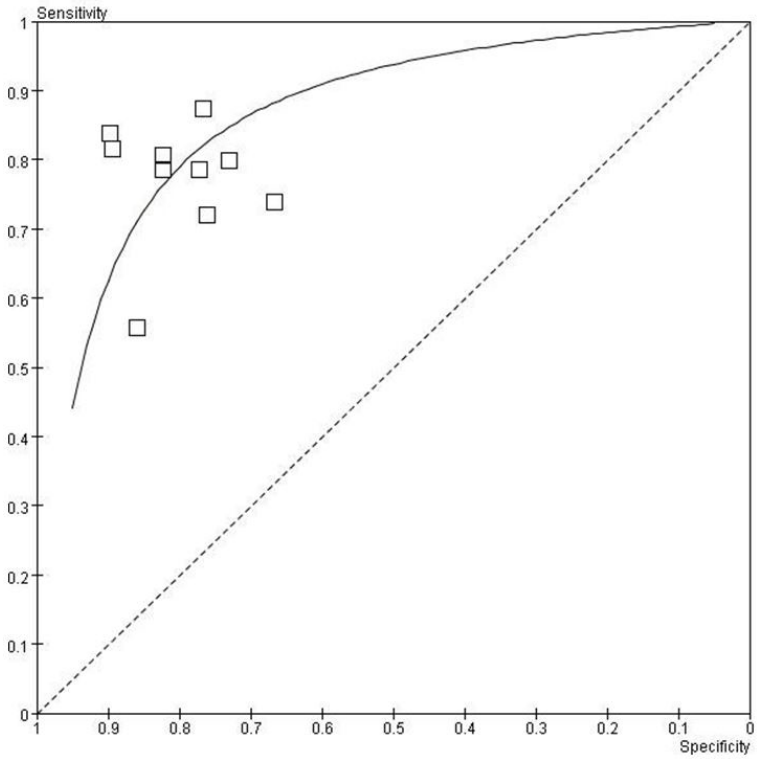

Figure 3: Summary Receiver Operating Characteristic (SROC) curve of machine learning for the prediction of acute respiratory distress syndrome

A Spearman rank correlation was performed as a further test for the threshold effect and was determined to be 0.163 (P=0.492), which indicated that there was an absence of a notable threshold effect in the accuracy estimates among individual studies.

The results of meta-regression indicated that ML modality was not strongly associated with accuracy (P=0.217), it had comparably high Sen estimate as follows: ANNs(0.785), ANNs+GA(0.800), XGBoost (0.719), random forest (0.736), SVM (0.873), deep learning (0.720), NLP (0.815) and CART (0.839) respectively.

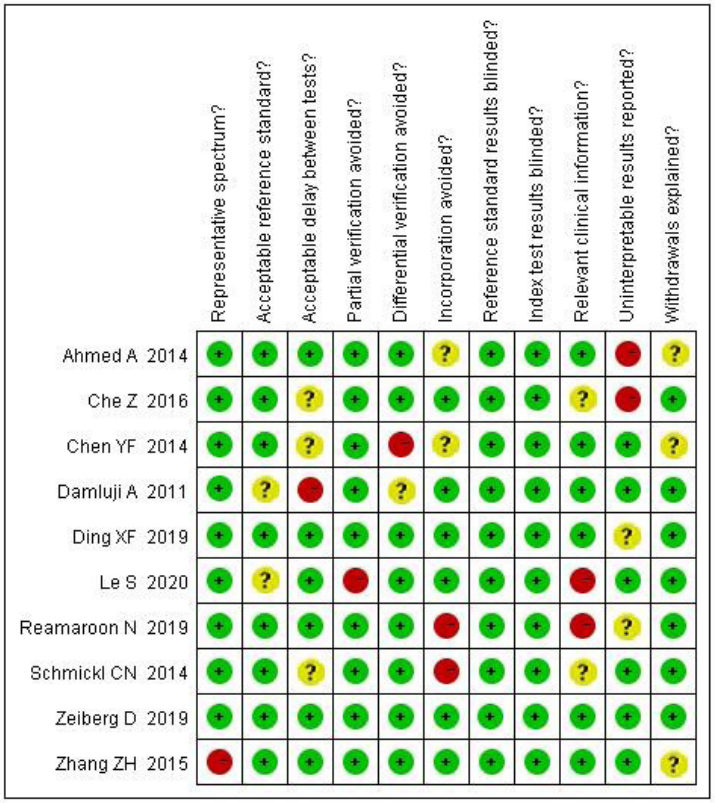

Figure 4: Assessment of methodological quality. Methodological quality was assessed according to the revised tool for QUADAS-2 (green+, yes; red-, no; yellow?, unclear)

The quality assessment was moderate in sixteen studies according to QUADAS-2 items, and the results of the distribution of the study design are shown in figure 4. Overall, the studies had good applicability with most cohorts enrolling patients with the target condition (potential ARDS) and had the same reference test (final discharge diagnosis). The summarized evidence had a GRADE quality evaluation as moderate (based on the GRADE scale of very low to high).

Discussion

ARDS is one of the major public health concerns because it is lethal, prevalent, and costly. It has emerged as a global burden due to higher morbidity and mortality [29-31]. Additionally, lengthy hospital stays due to ARDS are several times as common as for any other condition[32]. However, early and accurate diagnosis and treatment of ARDS has shown an association with improved patients outcome, reduced mortality rate, and decreased cost of care [33,34]. The strategy in improving the outcome of patients with ARDS was limited, and the mortality of ARDS patients remains still too high, specially after the development of ARDS into a serious condition. Thus, in terms of research priorities, it is important to change the treatment of ARDS into the avoiding of ARDS. ML have been recognized as a kind of novel method to predict the mortality of ARDS [24,27].

We conducted a meta-analysis to investigate the performance of ML for evaluating the mortality of ARDS. The overall pooled estimation showed that ML performance for early recognition mortality of ARDS and non-ARDS patients performed well. In order to determine the generalizability of ML algorithm for ARDS prediction to different modality, ML also demonstrated a good performance when used with different data-sets with varying types and frequencies of patient's measurements. The findings of our study suggest that the strong predictive performance of ML would be helpful to decrease ARDS-related in-hospital mortality, and ARDS-related length of hospital stay. Since the diagnosis and evaluation of ARDS patients is always challenging due to preexisting organ dysfunction, treatment prior to admission, and concurrent organ support. But high sensitivity and specificity of the ML method could correctly and accurately evaluate the patients, provide supportive treatment, and improve patient outcomes. Implementation of ML prediction methods can make immense chance to measure patient's criteria quickly and easily and assessed repeatedly over time in patients at risk of ARDS.

Despite many attempts to evaluate ARDS patients, it is still difficult for healthcare providers to correctly recognize and evaluate this condition because of the complexity of the disease [35-37]. An ideal situation is needed where minimal data is required, and data is routinely collected. ML method has the potential to use routine vital sign data to recognize ARDS patients' hours before it deteriorates.

Several studies have used ML algorithm, which uses the most common variables obtained from electronic health records to correctly predict and evaluate ARDS patients in the hospital [21,24,26,28]. Features for predicting ADRS patients among the included ML prediction models are known to be associated with the risk of mortality of ARDS. Furthermore, the ML models helped to identify well-known risk factors for ARDS even among the noise of many unrelated variables [37,38].

ML based ARDS evaluation system is designed to assist doctors in diagnosis, treatment, and patient's management in the intensive care units or emergency. Automated machine learning tools may be beneficial for doctors with a complex and difficult evaluation of ARDS by analyzing the current trends and correlations between vital sign measurements. As widely available traditional methods often suffer from low sensitivity or specificity and fail to predict patients with a higher risk of ARDS, ML models with higher accuracy may provide early warning signals which evaluate ARDS patients, help supportive treatment, and open the door to prevent the progression of the condition.

The meta-analysis was based on a rigorous literature search, which resulted in the inclusion of ten articles, and a validated appraisal tool was used to determine the risk of bias of these included studies. Still, there are some limitations. First, All the included almost common variables for the evaluation of ARDS but variables were not categorized according to their importance. Although, ML prediction model has ability to provide which variables are most useful for evaluation ARDS patients. The best ML model is to include precise and accurate variable selection for predicting ARDS patients. Second, some studies were specifically excluded because of incomplete data reporting (unable to construct a 2×2 table). There were also recurrent sources of bias on three of the four items of the QUADAS tool, which shows poor reporting of participants' characteristics and a study design for the included studies. Funnel plot or Egger testing that were used in publication bias were controversial because there were many reasons that could cause the asymmetry, such as opportunity, heterogeneity, effect of choice, the choice of measurement precision, *et al.* [39,40]. The experience of clinical epidemiology was of little help to judge result; subjective visual judgment was the main method. The following factors may lead to inefficiency of funnel plot or egger testing: 1) many factors lead to asymmetric funnel plot, which may be more heterogeneity rather than publish bias. In meta-analysis, it is difficult to ensure that various studies included in the analysis use the same method and the same quality. There is no guarantee that the patients owned the same disease severity, even the same personality traits, such as culture, geographical and racial differences were difficult to control. So we have no reason to expect the scatter diagram to be a symmetric shape of a funnel; 2) the effect size will offer great influence on graphic shapes; 3) if there were some potential relations between the size of sample size and effect size, the wrong conclusions could be drawn. Finally, while the two raters were fairly concordant when evaluating the risk of bias ($\kappa>0.50$), one item was less concordant. However, agreement was easily obtained between the two raters and the initial disagreements were mostly related to adherence to the defined standard.

Conclusion

In conclusion, the use of ML resulted in High predictive power, considering its excellent sensitivity and specificity values, ML may be useful as an initial triage tool to predict or rule out ARDS. Although the results look promising, there is a need for more randomized controlled trials evaluating the efficacy of ML in patients with ARDS only to truly unravel the potential of this technique. Meanwhile with the increasing prevalence of "big data" electronic health records, ML algorithms can be continuously refined, and its diagnostic accuracy may improve further with larger datasets of more patients and clinical variables. Refinement of current ML algorithms and technologies may improve further the sensitivity and specificity in prediction ARDS to expedite appropriate treatment.

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