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AIMS AND SCOPE

The primary aim of the *World Journal of Critical Care Medicine* (*WJCCM*, *World J Crit Care Med*) is to provide scholars and readers from various fields of critical care medicine with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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Artificial intelligence and computer simulation models in critical illness

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Abstract

Widespread implementation of electronic health records has led to the increased use of artificial intelligence (AI) and computer modeling in clinical medicine. The early recognition and treatment of critical illness are central to good outcomes but are made difficult by, among other things, the complexity of the environment and the often non-specific nature of the clinical presentation. Increasingly, AI applications are being proposed as decision supports for busy or distracted clinicians, to address this challenge. Data driven "associative" AI models are built from retrospective data registries with missing data and imprecise timing. Associative AI models lack transparency, often ignore causal mechanisms, and, while potentially useful in improved prognostication, have thus far had limited clinical applicability. To be clinically useful, AI tools need to provide bedside clinicians with actionable knowledge. Explicitly addressing causal mechanisms not only increases validity and replicability of the model, but also adds transparency and helps gain trust from the bedside clinicians for real world use of AI models in teaching and patient care.

Key words: Artificial intelligence; Digital twin; Critical illness; Predictive enrichment; Causation; Simulation models

Core tip: Widespread implementation of electronic health records coupled with increased

computer power has led to the increased use of artificial intelligence and computer modeling in clinical medicine. To be clinically useful, artificial intelligence models need to be built on accurate data, take into consideration causal mechanisms, and provide actionable information at the point of care.

INTRODUCTION

The complex nature of critical illness calls for an exploration of alternative approaches to assist clinicians in their timely diagnosis and management. Artificial intelligence (AI) applications have transformed various human domains from economics to traffic and have recently been introduced into health care.

AI IN HEALTH CARE

Widespread implementation of electronic health records (EHRs) has led to the increased use of AI and computer modeling in clinical medicine. The hope is that these techniques will prove superior to traditional epidemiologic and statistical approaches and will unlock insights that lead to the development of new treatment recommendations and prediction models. AI can be defined as the field of computer science that enables computers to perform the human cognitive tasks[1]. The interest in AI and systems science methodologies in the research community has grown rapidly in recent years[2]. Specific AI applications of interest to critical care include machine and deep learning algorithms, "in silico" simulation models, and "digital twins".

Machine learning

Machine learning (ML) is an application of AI that develops statistical analysis models using computational technologies applied to big data[3]. The following learning techniques could be used: (1) Supervised learning techniques include but are not limited to linear regression, decision trees, and Naive Bayes. The models developed based on these are normally used for anomaly detection with the use of algorithm approximating a known output with a higher accuracy from a labeled data set, for example: Electrocardiogram interpretation by the automated machine or detection of a lung nodule from a chest X ray or a CT scan based on pattern recognition[4,5]. The aim of models developed using this technique is to decipher rules and latent relationships within data. "Support Vector Machine" is an example of supervised ML algorithm which is used for both classification and regression challenges and give a different dimension to the ensemble models. They are crucial in cases which require high predictive power but these algorithms are hard to visualize due to the complexity in formulation; (2) Unsupervised learning: Unsupervised ML models are developed using clustering techniques which includes segmenting data by some shared attributes, detecting anomalies that do not fit to any group and simplifying datasets by aggregating variables with similar attributes. The main goal is to study and determine the intrinsic and often hidden structure of the data. These models use algorithms on unlabeled data with no outputs to predict but are exploratory and intend to find naturally occurring patterns within the data[6]. This technique can be condensed in two major types of problems that unsupervised ML models try to solve, clustering and dimensionality reduction; (3) Semi-supervised learning uses a dataset with unlabeled as well as labeled data to increase the learning precision and appropriate prediction of label function. Further the model is trained and retrained with the estimated labels from the previous step[7]. These semi-supervised ML models are commonly used in medicine such as in voice recognition (medical dictation applications), data mining, and video surveillance (used in e-ICUs)[8,9]; and (4) Reinforcement learning: Reinforcement ML algorithms learn by observing the result of an action taken by the algorithm and applying a similar algorithm where the data are limited or missing[10]. The algorithm iteratively learns from previous response (reward or penalty) and acts with a goal to receive maximum reward in the future.

Deep learning

Deep learning (DL) refers to the automatic determination and processing of the parameters in a network, on the basis of experience. DL is a ML technique that is designed with multiple layers of neurons, including input and output layers, and so-called "hidden layers"[11]. This idea of hidden layers (neural network) is inherited from a popular engineering and cognitive science topic since the 1980s[12,13]. The input data is passed through the layers, and the complexity of output function increases from layer to layer. In the recent past, the use of DL models in medicine has introduced the idea of data analytic modeling from expert-driven feature to data-driven feature. Large and complex databases (with longitudinal event sequences and continuous data points) have made it possible to train complex DL models. These models developed from large and complex databases with multiple hidden neural layers provide limited transparency to the users and are aptly described as "black box" models. The user of "black box" AI knows inputs and understands outcomes of the model, but how the output value was generated is unknown. These DL models are most commonly utilized in the field of medicine for following categories of analytical tasks: (1) Disease detection or classification, where DL models are used to detect a specific disease(s) with the help of data mining from EHR[14]; (2) Sequential prediction of clinical events, where DL models predict future clinical events learning from the previous event sequences[15]; (3) Concept embedding, where DL models derive feature representation of clinical concepts algorithmically from the EHR data[16]; (4) Data augmentation, where DL models create realistic data elements for the use in clinical research or otherwise based on real EHR data[17]; and (5) EHR data privacy, where DL models derive techniques to protect patient EHR privacy by de-identification[18].

In simpler words, it would be easier to understand the relationship of AI, ML and DL by visualizing them as 3 concentric circles with DL being the innermost circle which is a subset of ML. ML in turn is a part of the greater all-encompassing concept of AI (thus AI fits inside both ML and DL).

In silico simulation models and digital twins

"In silico" experimentation or simulation involves mathematical and computer based exemplifications to construct models[19]. Computer based experiments can then be carried out to conduct investigations of hypotheses in a virtual environment without actually involving human subjects. The Archimedes model illustrates the use of mathematical techniques to reproduce the complex nature of disease[20]. The core model is a set of ordinary differential equations, which represent the physiologic, clinical, and social pathways that are relevant to diabetes and diabetes-related complications. The use of causal pathways (*i.e.*, Disease Acyclic Graphs) distinguishes Archimedes from conventional, associative AI models[17]. Digital twin is a type of simulation model that combines current data from the object with its simulation model to enhance insight and assist with decision making[21,22]. The digital twin has proven to be effective in industry and transportation, such as gas turbine fleet, rail fleet, and production line. The advantage of this approach is the ability to get the representative operational updates from the real-world object that allows model to give an accurate prediction and to give the feedback to the real-world state directly to make operational changes.

AI IN CRITICAL CARE

Critical illness offers a number of advantages for the developers of AI models compared to chronic disease, such as the availability of large quantities of qualitative and quantitative data and relatively short trajectory of critical illness to a stable outcome. This results in the possible iterative testing of hypotheses raised by simulation modeling in independent patient cohorts. For example, recently, a group of computer scientists and clinicians from the Imperial College, London, United Kingdom used an AI approach to develop a decision support model aptly named AI Clinician[23]. Using reinforcement learning (RL), AI Clinician is designed to assist with optimal treatment interventions for sepsis in real-time. It was developed and validated in two clinical databases: MIMIC-III and e-ICU research database[24,25]. Similar methodology has recently been applied to the continuous prediction of acute kidney injury (AKI)[26]. Tools that are developed based on the current AI models have low specificity in predicting the intervention points for real life sepsis patients. This is one of the major obstacles faced by AI models for treating the critically ill patients. While most of the currently devised models are based on the retrospective data from the data banks, the accuracy and performance of these algorithms on real-time data

may not achieve the same level. Patient privacy concerns and question of responsibility may preclude rapid integration of AI models into current ICU practice. High heterogeneity of patients and their specific needs could be easily illustrated by managing a patient on mechanical ventilation. "Intelligent" ventilation modes may do more harm than good without thorough supervision by a specialist.

The above examples highlight a new approach to predictive and prognostic analytics in the area of critical care. Although these models yielded clinically plausible results, major shortcomings limit inferences and use in the real world of bedside clinical medicine. First, built exclusively from retrospective EHR data, the models suffer from missing data and imprecise timing (back charting) particularly during the initial, golden hours of critical illness. Not unlike retrospective studies using traditional methods (logistic regression), the output results are only hypothesis raising and require prospective confirmation.

PROGNOSTIC (ASSOCIATIVE) *VS* PREDICTIVE (ACTIONABLE) AI MODELS

While offering marginal improvements in performance over traditional epidemiological or logistic regression approaches, associative AI models generally underperform in the live clinical setting and struggle to breach the threshold of usefulness for most clinicians[27]. Even accurate prognostic enrichment (classifying patients with high or low likelihood of death or AKI) is of limited value to the bedside clinician. For example, the prediction model of AKI does not provide any predictive enrichment with regards to potential intervention[26]. For example, will my patient benefit from a red cell transfusion, or continuous *vs* intermittent renal replacement?

Predicting the risk *vs* the benefit of a particular treatment (*i.e.*, actionable AI) is more difficult. Differences between associative and inquisitive/actionable AI are highlighted in Table 1. In contrast to "black box" associative AI, actionable AI models should explicitly address causal relationships[28]. Directed acyclic graphs – (DAG) approach has been increasingly used to address causal relationships in different research domains[29]. DAGs facilitate integration of expert knowledge into data driven AI models and are well suited for building advanced AI algorithms and simulation models.

Bayesian networks are DAGs whose nodes represent variables in the Bayesian sense: They may be observable quantities, latent variables, unknown parameters or hypotheses. Edges represent conditional dependencies; nodes that are not connected (no path connects one node to another) represent variables that are conditionally independent of each other. Each node is associated with a probability function that takes, as input, a particular set of values for the node's parent variables, and gives (as output) the probability (or probability distribution, if applicable) of the variable represented by the node. Directed acyclic graphical model is a probabilistic graphical model (a type of statistical model) that represents a set of variables and their conditional dependencies – also known as the Bayesian network Model.

Unidirectional arrows of DAGs are based on known causal effects (and prior knowledge) (Figure 1). DAGs enable clear representation and better understanding of the key concepts of exposure, outcome, causation, confounding, and bias. DAGs are built as simple integers of physiology as a basis to building complex patterns for seamless functionality of a simulation model and AI application. One of the advantages of using multiple basic DAGs to build a complex model is that, the model can be easily disassembled as individual components (DAGs) to ensure that the complex model can be better understood and refined as necessary.

CONCLUSION

In a complex critical care environment clinicians are challenged with making decisions with a high degree of uncertainty under time constraints. Data driven associative AI models hold promise for better prognostication and to augment the diagnostic process but thus far have not been proven useful for bedside clinicians. Transparency of the model in terms of analytics and algorithms is important for patient safety and to earn the trust of the treating clinician[30]. Actionable AI models are more challenging to build and require explicit consideration of causal mechanisms. Accurate prediction of the response to treatment or intervention without exposing the patients to potential risks is an ultimate AI challenge for the benefit of patient and clinicians alike.

Table 1 Differences between associative artificial intelligence and actionable artificial intelligence models

Models based on associative artificial intelligence	Models based on actionable artificial intelligence
These applications are built using available historical public or institutional data repositories[26,31,32].	These applications are built more often on the prospectively collected data points, predicting risk *vs* benefit of a particular treatment or intervention[17,30,33,34].
Almost always based on retrospective data[35,36].	Developed using the data points that are collected prospectively in real-time[30,34].
Purely data driven associative models often without explicit consideration of causal pathways[37-39].	These models are developed with an understanding based on the underlying causal pathways, therefore providing greater clinical utility and accuracy[40-42].
Representative examples: Development and validation of a data driven tool to predict sepsis based on vital signs by Mao *et al*[43]. Provides no actionable benefit to the bedside clinician. Similarly, a model developed to predict AKI in a patient based on retrospectively collected dataset from electronic health records by Tomasev *et al*[26]. The model was associated with high false positive alerts (2 false positive alerts for each true alert).	*Representative examples*: Improving the safety of ventilator care by avoiding ventilator-induced lung injury. Electronic algorithm based on near real-time data and notification of bedside providers giving actionable information, developed by Herasevich *et al*[33]. Artificial neural network based model developed for forecasting ICP for medical decision support, by Zhang *et al*[42]. This model provided actionable treatment planning for patients based on the predicted future trends of ICP.

AKI: Acute kidney injury; ICP: Intracranial pressure.
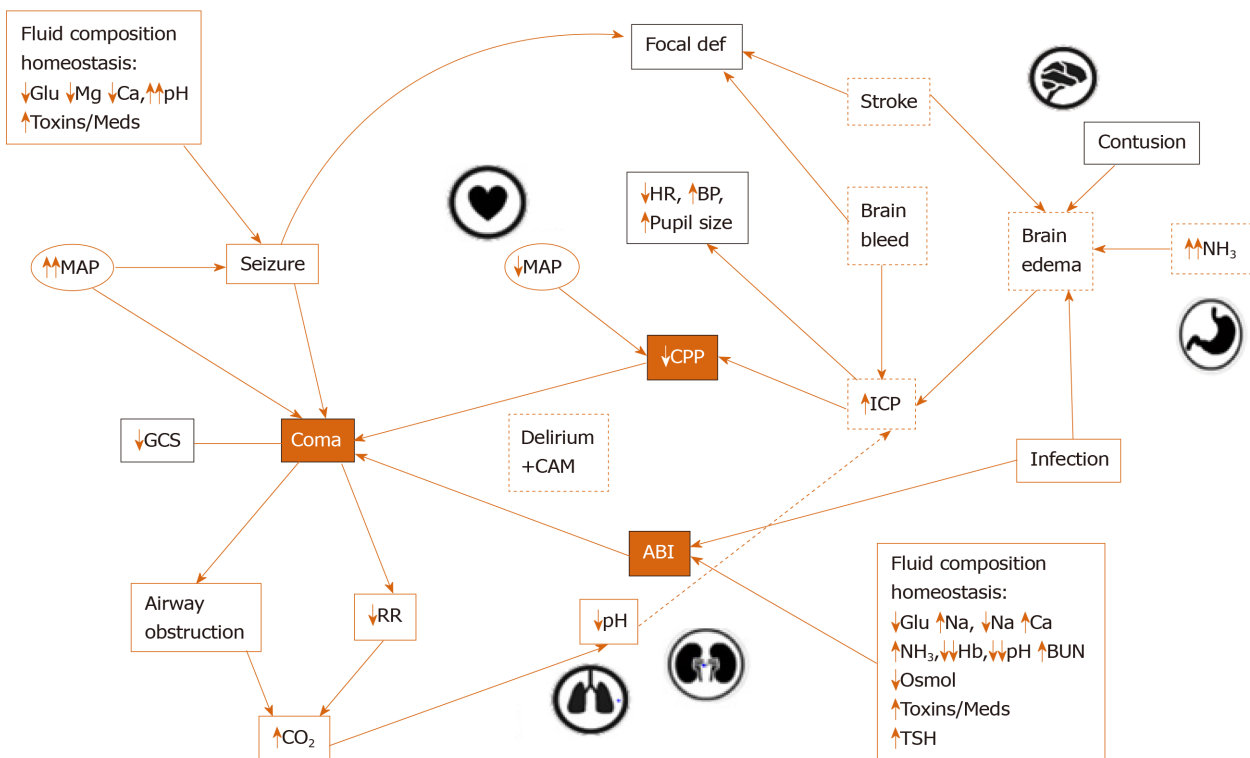

Figure 1 Directed acyclic graph of acute brain failure. Orange boxes: Concepts; Orange solid border: Actionable clinical points; Orange interrupted border: Semi-actionable clinical points. GCS: Glasgow coma scale; MAP: Mean arterial pressure; Glu: Serum glucose; Mg: Serum magnesium; Ca: Serum calcium; Meds: Medications; HR: Heart rate; BP: Blood pressure; Focal Def: Focal neurological deficits; ICP: Intracranial pressure; NH$_3$: Ammonia; Na: Serum sodium; Hb: Serum hemoglobin; BUN: Blood urea nitrogen; Osmo: Serum osmolality; TSH: Thyroid stimulating hormone; CO$_2$: Serum carbon dioxide; CPP: Cerebral perfusion pressure; ABI: Acute brain injury; CAM: Confusion assessment method for intensive care unit.

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