**Artificial Intelligence for clinical decision support in Critical Care, required and accelerated by COVID-19**

Words: 1255

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**Key words**: Artificial Intelligence, COVID-19, Innovation, Machine Learning, Monitoring

**Conflict of interest**

M. Jansson, J. Rubio and J. Rello declare no conflict of interest related to the current manuscript. R. Gavaldà is CEO and co-founder of Amalfi Analytics, a startup that creates platforms for healthcare analytics using Machine Learning.

**Figure Legend**: The fusion of free text data, speech recognition, and sensors in addition to vital signs, biomarkers, and demographic data from heterogenous data sources can improve Machine Learning-based clinical decision making in ICUs.

**Artificial Intelligence for clinical decision support in Critical Care, required and accelerated by COVID-19**

Artificial Intelligence (AI) is transforming medical practice and precision medicine in Intensive Care Unit (ICU) [1]. The adoption of AI in healthcare began with the development of expert systems in the early seventies. Such systems have been utilized for centralized monitoring (e.g., tele-ICU), automated surveillance (e.g., VAEs, sepsis), and most recently, to help with digital contact tracing amid the COVID-19 pandemic.

The current pandemic is accelerating the need to take advantage of AI to make real time clinical and operational decisions, wisely integrating the vast amount of heterogeneous data and emerging knowledge generated in the critical care environment [1]. Safe, effective, efficient, and ethical clinical management of COVID-19 patients in ICUs urgently requires bringing AI capabilities to the bedside.

Prior to COVID-19, up to 20 million people annually required ICU admission and mechanical ventilation (MV) [2]. The burden for critical care services has risen exponentially in response to the COVID-19 pandemic [3]. Facing this "new reality", ICUs and emergency departments (EDs) need to be re-designed. For instance, creative ways of accommodating frequent ventilator adjustments while reducing the risk of exposure to health care workers need to be found (HCWs) [4]. AI, big data, and machine learning can help health care systems respond to these unprecedented challenges. If appropriately designed and deployed, AI can allow for early diagnosis (e.g. computer-aided methods to help radiologists identify COVID-19 specific lesions in chest X-rays), distance monitoring, and can assist the clinical decision making process, and improve efficiency.

Predictive analytics can be used to estimate the probability of either presenting (diagnostic models) or developing a particular disease or outcome (prognostic models) [1]. *Diagnostic models* have been proposed in a variety of clinical situations including early detection or stratification of sepsis [5], bacterial and viral infections (e.g., COVID-19) [5], and delirium in the ICU [5], as well as pulmonary embolism in primary care [6]. *Prognostic models* have focused on predicting ICU-related mortality [7], infections (e.g., positive blood culture, MRSA) [5], responses to treatments [5], antibiotic resistance [5], asynchronies during assisted ventilation [8], prolonged MV [9], extubation failure [10], and death in influenza [11], COVID-19 [12, 13], and community-acquired pneumonia [14]. The best performance were observed in models that rely on clinical, laboratory, and radiological variables [14]. Most of these studies, however, have not included continuous physiological signals (e.g., ventilator parameters, vital signals) for prediction [1]. Indeed, such information would substantially improve prediction performance  [15].

Beyond predicting specific outcomes, one should expect advances in the direction of predicting the entire temporal evolution of a patient. Techniques such as structured output prediction or latent embedding have been successfully used both in the ICU and elsewhere [16, 17]. This approach can be used for developing personalized patient management and treatment plans, based on the success on previous patients with similar prognosis.

AI and machine learning (ML) have largely been applied to the data collected since the beginning of the COVID-19 pandemic. Traditional epidemic models have described the spreading of a contagious disease in a population using differential equations. Most recently, AI has been used to predict COVID-19 incidence and evaluate the impact of mitigating measures such as population confinement and social distancing [18]. Geolocated critical care demand prediction, optimal hospital resource planning, and intelligent patient flow management with decision support algorithms can also be achieved by integrating real time clinical data with population statistics and health interventions. Computer-assisted detection systems can be used for early identification, grading, and monitoring of infectious and noninfectious lung diseases. Interestingly, they can be also be used to distinguish viral pneumonia from bacterial pneumonia [19]. Most recently, however, ML techniques have focused on detecting COVID-19 infections in chest X-rays and CT scans [20, 21]. Overall sensitivity of CT scan have ranged from 57%–100% for symptomatic and 46%–100% for asymptomatic COVID-19 patients [21].

The worldwide shortage of personal protective equipment has promoted the utilization of robotic technologies to minimize human-to-human contacts and the workload of healthcare workers. A robotic telepresence is seen as a natural successor to tele-medicine. Robots have also been used to automate and scale up testing capabilities, with rapid prototyping, development, and validation of automated clinical diagnostic tests for COVID-19 [21]. Robot-assisted rehabilitation has been shown to be more effective than conventional therapy alone to improve functional recovery in critically ill patients whereas the effectiveness of robot-assisted endovascular/intravenous catheterization and tracheal intubation, for instance, are under investigation [23, 24, 25].

Novel sensor array techniques have been used in infectious and noninfectious lung diseases. For instance, exhaled breath biomarkers (e.g., volatile and nonvolatile components) are promising alternatives to traditional microbiological diagnostics. Commercially available electronic nose sensors have been developed to diagnose ventilator-associated pneumonia (with and without Pseudomonas aeruginosa) [26]. Using several ML algorithms, a high diagnostic accuracy has been detected therein. In the future, detecting, tracing, and managing new viral outbreaks will require deploying inexpensive and ubiquitous sensor networks. Intelligent biosensors may be become part of our smart cities and buildings, integrated in our environment, air, sewage, and waste management systems. Wearable personal biosensors will monitor our bodies while synthetic molecular biosensors will be part of our tissues and cells.

Engineering biology capabilities are exponentially accelerating as DNA/RNA reading and writing costs rapidly approach zero. Every mutation of COVID-19 has been sequenced and synthesized in record time, and many regions in the world are beginning to integrate WGS human data with EHR systems for personalized medicine diagnostics and treatment [27]; research projects are now correlating genomic biomarkers with infection severity and prognostic treatment efficacy [28, 29]. ML allows searching libraries of available drugs and known molecules, accelerates effective vaccine and treatment development, enables digital modeling and testing, and engineering antibodies. Furthermore, by sharing information and using standards, synbio factories are able to locally manufacture physical biomolecules designed elsewhere.

Assessment tools for AI and robotics need to be further developed [30] and the standardization of data and semantics coding, integration, and usability have to improve. In addition, signal processing and thus, signal quality control at the bedside have to be developed [1]. Better human interpretability, explainability and traceability of ML predictions and AI decisions are also required. While ML capabilities will be progressively embedded in every physical system in the ICUs, from sensors to medical devices to clinical and operational information systems, it is important and urgent to address the need of developing new AI management structures in our health systems, like the Clinical AI Department [31], that play an essential role in the implementation, utilization and enhancement of the infrastructures that underlie AI solutions. Human-AI cooperation in ICUs is a growing must, which is accelerated and needed to treat COVID-19 and the next pandemics patients. Currently, due to poor interoperability between platforms, legal barriers and questions of data reliability, only a small fraction of the clinical data generated in the ICUs are accessible for research [1].

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