Intensive Care Unit Telemedicine in the Era of Big Data, Artificial Intelligence, and Computer Clinical Decision Support Systems

Ryan D. Kindle, MD[a,b,1], Omar Badawi, PharmD, MPH, FCCM[a,c,d,2],
Leo Anthony Celi, MD, MS, MPH[a,b,*,1],
Shawn Sturland, MBChB, FANZCA, FCICM[a,e,1]

KEYWORDS

• Telemedicine • ICU • Machine learning • Clinical decision support systems

KEY POINTS

- Telemedicine intensive care units (tele-ICUs) cover more than 11% of ICU beds in the United States and produce enormous quantities of data, which can be used to create machine learning algorithms.
- Tele-ICU systems including clinical decision support systems have been shown to improve adherence to ICU best practices.
- Machine learning algorithms exist for sepsis detection, sepsis management, mechanical ventilation, false-alarm reduction, and ICU outcomes; validation using external data sets is important.
- Translating ICU machine learning algorithms to the tele-ICU requires the ability to generalize and adapt to a tele-ICU work flow that manages larger populations.

Disclosure: The Laboratory of Computational Physiology receives research funding from Philips Healthcare (United States). Dr O. Badawi is an employee of Philips Healthcare.
[a] Laboratory for Computational Physiology, Massachusetts Institute of Technology, Cambridge, MA, USA; [b] Department of Pulmonary, Critical Care, and Sleep Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA; [c] Patient Care Analytics, Philips Healthcare, Baltimore, MD, USA; [d] Department of Pharmacy Practice and Science, University of Maryland School of Pharmacy, Baltimore, MD, USA; [e] Department of Intensive Care, Wellington Hospital, Wellington, New Zealand
[1] Present address: E25-505, 77 Massachusetts Avenue, Cambridge, MA 02139.
[2] Present address: 217 East Redwood Street, Suite 1900, Baltimore, MD 21202.
* Corresponding author. Massachusetts Institute of Technology, E25-505, 77 Massachusetts Avenue, Cambridge, MA 02139.
E-mail address: lceli@mit.edu

Crit Care Clin 35 (2019) 483–495
https://doi.org/10.1016/j.ccc.2019.02.005 criticalcare.theclinics.com

INTRODUCTION

Over the last half-century, the telemedicine intensive care unit (tele-ICU) has grown from a daily video conference to a comprehensive high-bandwidth system connecting more than 11% of intensive care unit (ICU) beds in the United States to remote clinicians with real-time exchange and archiving of extensive patient data fed through algorithmic clinical decision support systems (CDSSs).[1,2] Machine learning (ML) has grown in parallel with the increasing availability of powerful computational resources. ML algorithms such as neural networks can process enormous quantities of data through multiple layers of features to elucidate novel interactions (**Fig. 1**). This article reviews the history of tele-ICU, examines the current state of ICU and tele-ICU CDSS (which can encompass predictive, detective, and prescriptive algorithms), and presents an overview of ML applications in the ICU that may be suitable for tele-ICU adaptation. In addition, it discusses issues to be considered when implementing tele-ICU CDSS, including staff perception and acceptance, human factors engineering, outcome measurement, and the need for rapid and continuous validation throughout the CDSS lifecycle. The development of clinically useful CDSS is not a simple task and its adaptation for the tele-ICU can be a formidable challenge, but the increasing accessibility of ML algorithms and large ICU databases for CDSS development and validation provides hope that a renaissance in tele-ICU CDSS may be coming soon.

HISTORY

Telemedicine Intensive Care Unit

The first implementation of tele-ICU care was in 1975, as a 2-way audiovisual link to provide remote intensivist consultations, with real-time data collected manually by consultants and outcomes obtained from a post hoc chart review.[1] The technology used did not make any provisions for the automatic acquisition, hardcopy transmission, or electronic storage of patient data. Furthermore, only 30% of the recommendations made by the remote intensivist were executed and the limited amount of time spent in direct communication with bedside physicians was considered a

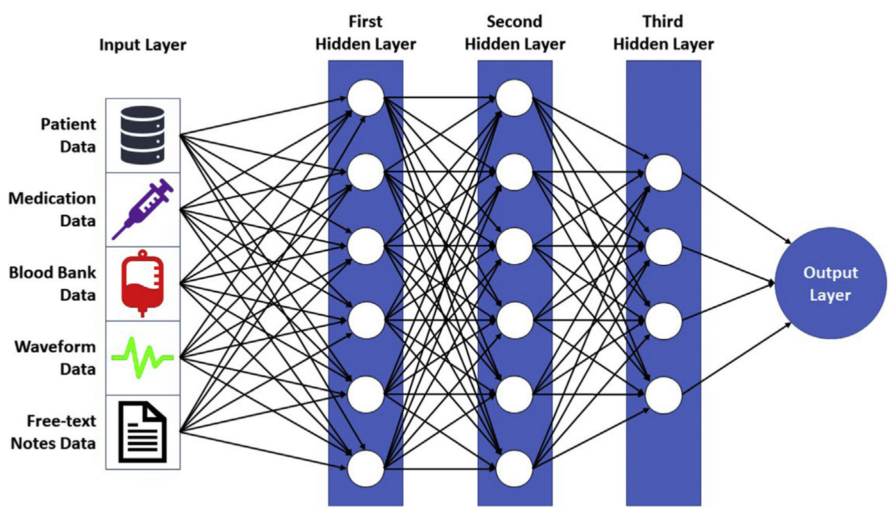

Fig. 1. Neural network example using readily available electronic medical data.

significant barrier to care.[3] These difficulties foreshadowed many of the challenges in developing effective tele-ICU CDSS.

By 1997, advancements in communications technology facilitated the deployment of a tele-ICU system capable of rapidly transmitting comprehensive patient data. Rosenfeld and colleagues[4] described a system providing access to real-time bedside monitor data, laboratory data, scanned hardcopy data (eg, electrocardiograms), daily video conferencing rounds with bedside physicians, twice-daily nursing discussions, and rapid bidirectional communication. Compared with 2 historical baseline periods, the implementation period had significantly lower severity-adjusted ICU mortality, severity-adjusted hospital mortality, ICU complication rate, and ICU length of stay (LOS).

It was evident at the time that these systems needed to incorporate tools that alleviate the cognitive burden on critical care providers. CDSS were developed using evidence-based clinical practice guidelines and protocols, disseminated using Web-based tools, and integrated into order entry systems.[5] Predictive alerts were developed to detect physiologic trends using vital signs and laboratory data before an overt clinical deterioration, allowing a small team of providers to monitor many patients. The clinical information system structured provider input, which was fused with the abundant clinical data generated during routine care to develop a data warehouse for future data mining and analysis.

As of 2014, continuous tele-ICU coverage was available for 11% of nonfederal hospital ICU beds for adults.[2] With tele-ICU coverage projected to grow a rate of 1% per year, it may have surpassed bedside intensivist coverage since then. Koninklijke Philips eICU, the successor to the Rosenfeld and colleagues'[4] system, is the predominant tele-ICU implementation in the United States, covering 99.2% of tele-ICU deployments based on Medicare data through 2010.[6]

Machine Learning in Critical Care

As the tele-ICU came of age, researchers developed novel uses for ML in critical care. Hart and Wyatt[7] assessed the ability of neural networks trained on 174 cases of chest pain to predict myocardial infarctions in a validation set of 73 cases, but found a false-negative rate of 27%. Doig and colleagues[8] developed a back-propagation associated-learning neural network using 27 features from 422 patients to model ICU mortality, but found it equivalent to logistic regression when used on training and validation sets. The investigators suggested larger data sets would allow prediction of ICU mortality with greater than 95% sensitivity and specificity. ML methods were applied in multiple other critical care contexts over the next 15 years with limited impact because of the small underlying data sets and lack of external reproducibility.

The last decade's advances in computing power and the availability of large clinical databases have allowed dramatic advancements in the application of ML to medicine. Ting and colleagues[9] described a deep learning system trained on 494,661 retinal images that accurately classifies diabetic retinopathy, possible glaucoma, and age-related diabetic retinopathy with an area under the receiver operating characteristic curve (AUROC) greater than 0.93 in all cases compared with professional graders. Moreover, external validation had an AUROC range of 0.889 to 0.983 using 10 additional data sets.

Electronic medical record (EMR) and tele-ICU adoption have exponentially increased the amount of digitally archived medical data. The large, rich, heterogeneous data sets that result have been used to develop novel clinical insights.[10,11] The deidentification of data sets has facilitated dissemination of data that were previously sequestered, such as the Medical Information Mart for Intensive Care database

(MIMIC-III)[12] and the eICU Collaborative Research Database (eICU-CRD).[13] The development of generalizable medical ML algorithms will only be possible using such large, comprehensive, heterogeneous, and granular data sets.

STATE OF CLINICAL DECISION SUPPORT SYSTEMS IN THE TELEMEDICINE INTENSIVE CARE UNIT

All tele-ICU outcome studies have been observational with predominantly pretest/posttest designs.[14,15] Tele-ICU implementations have differed significantly between studies and findings have been mixed. Highlighting the importance of effective implementation through clinical transformation, 2 major studies that failed to show significant benefit reflected poor cultural adoption: the tele-ICU team was prohibited from managing patients outside of code situations in approximately two-thirds of intervention patients.[16,17] Furthermore, studies have precluded analysis of the relative impact from individual factors in tele-ICU care, including CDSS.[18] Two studies met inclusion criteria for a systematic review, which found that tele-ICU care was associated with reductions in ICU mortality, hospital mortality, ICU LOS, and hospital LOS.[19]

In 2011, Lilly and colleagues[20] also found associations between tele-ICU care and increased adherence to best-practice guidelines (for prevention of venous thromboembolism [VTE], stress ulcers, cardiovascular complications, and ventilator-associated pneumonia) and lower risk of catheter-related bloodstream infection and ventilator-associated pneumonia. Lower tele-ICU mortalities persisted after adjusting for these differences, which were estimated to account for 25% of the hospital mortality and 30% of the ICU mortality declines. A 2014 multicenter pretest/posttest study further showed associations of tele-ICU care improvements in best-practice adherence and decreased mortality and LOS.[21]

It is reasonable to presume that CDSS deployment is a significant factor in improving best-practice adherence. Although the CDSS algorithms used in tele-ICU systems are proprietary, a number have been described in the literature. It is important to recognize that the work flow for tele-ICU clinicians is not identical to that of bedside staff, and therefore the design for tele-ICU CDSS may differ from bedside tools. Notably, a core feature of tele-ICU is population management, and many tools are designed to facilitate tele-ICU staff shifting roles as needed for a large population of ICU patients. Furthermore, no CDSS tool will improve outcomes without effective integration into work flow and a collaborative environment to support care at the bedside.

Patient Acuity

Williams and colleagues[22] described a 3-level color-coded acuity system for tele-ICU patients that incorporated time since ICU admission, vital sign stability, active titration and level of vasoactive agents, initiation of mechanical ventilation, emergent interventions, deescalation of therapies, safety concerns, and readiness for ICU transfer. The acuity category determined the frequency of tele-ICU nursing rounds and prioritized workflow. Other acuity scores for delirium, pain, and agitation evaluate ICU patients for corresponding factors related to screening, treatment, and adverse drug events, and present data in a dynamically changing dashboard for the population monitored.[23] However, the specific components are proprietary and not detailed in the tele-ICU literature.

Laboratory and Ordering Alerts

Tele-ICU deployments provided alerts for abnormal laboratory results before EMRs were widely used.[20] Medication dose adjustments can be prompted by creatinine clearance changes and computerized provider order entry can detect allergies and drug interactions.[5]

Best-practices Adherence

Routine monitoring of best practices based on clinical guidelines in domains such as VTE prophylaxis, stress ulcer prophylaxis, low tidal volume ventilation, β-blocker use, and glycemic control allows for real-time nonadherence notification and routine administrative auditing.[10] A retrospective multicenter study from 2009 to 2013 showed that adherence to best practices for VTE prophylaxis, low tidal volume ventilation, and glycemic control for tele-ICU patients significantly increased.[11] Remote screening with EMR prompting has been found to increase the likelihood of sedation interruption and spontaneous breathing trials, with an associated decrease in duration of mechanical ventilation, ICU LOS, and hospital LOS.[24] The rate of 3 hospital-associated infections did not differ despite remote screening for adherence to a ventilatory bundle and daily assessment of the need for central venous and urinary catheters.

Ventilator Management

Kalb and colleagues[25] studied the impact of tele-ICU–directed daily ventilator rounds in 11 hospitals with varying levels of ICU staffing. The rounds assessed adherence to low tidal volume ventilation but also addressed ventilator settings, sedation strategies, spontaneous breathing trials, and readiness for ventilator liberation. The intervention was associated with significant increase in low tidal volume ventilation adherence, from 29.5% before implementation to 44.9% after 9 months, and the improvement persisted 6 months later (52.0%). There was also an associated improvement in the Acute Physiology and Chronic Health Evaluation IV (APACHE-IV)–adjusted ICU mortality ratio (0.94 vs 0.67 after 9 months).

Sepsis Screening and Management

Rincon and colleagues[26] described the implementation of a tele-ICU nurse–driven program to facilitate early identification of patients with severe sepsis and prompt initiation of bundled care based on what were considered best practices at the time. From 2006 to 2008 the tele-ICU nurses manually performed 89,921 screens between 10 hospitals and identified 5437 patients with severe sepsis. Screening was associated with increases in timely antibiotic administration (74% vs 55%), serum lactate measurement (66% vs 50%), 20 mL/kg fluid bolus administration (70% vs 23%), and central line placement (50% vs 33%). The evolving definition of sepsis and its standard of care over the last several years exemplify a common issue in developing robust CDSS tools with validation for syndromes that are not firmly defined.[27]

Automated sepsis screens with 90% sensitivity and 80% specificity have reduced the burden of manually screening patients but still have a low positive predictive value because of the small population at risk.[27] Randomized controlled trials of automated sepsis monitoring systems in a single academic tertiary care center without tele-ICU found no significant differences in median time to new antibiotics, fluid administration, time to completion of a sepsis bundle or individual elements, ventilator-free days, ICU-free days, ICU LOS, hospital LOS, ICU mortality, and in-hospital mortality.[28,29] Nevertheless, automated sepsis screening remains an area of active research and development in the tele-ICU.[30]

Physiologic Instability Alerts

The proprietary algorithms implemented by tele-ICU providers have not been described in detail in the published literature. However, they claim the ability to detect early signs of physiologic instability and notify providers.[21] An association between shorter alarm response times and shorter ICU LOS was found based on observational data.[21] However, use of a tele-ICU model does not guarantee a timely response to physiologic instability alarms.[31]

Intensive Care Unit Readmission Risk

McShea and colleagues[32] reported the development of an initial retrospective exploratory cohort using 123,848 ICU stays between 2005 and 2007 from the Philips eResearch Institute (eRI) database to create a model predicting death or ICU readmission within 48 hours of ICU discharge. The logistic regression model was found to have a c-index predicting death of 0.89 and ICU readmission of 0.61.

Subsequently, Badawi and Breslow[33] described the development and internal validation of a different multivariable logistic regression model predicting death or ICU readmission within 48 hours of ICU discharge. The retrospective cohort was also derived from the eRI database taking 704,963 patients meeting inclusion criteria at 219 hospitals between 2007 and 2011, with 2:1 allocation to the development and validation. Of the initial 59 variables considered, the final model included 26 for death and 23 for ICU readmission, 8 of which were known at the time of admission. The readmission model had a median AUROC of 0.71, whereas the mortality prediction model had a median AUROC of 0.92; both performed similarly in the development set and validation set. Compared with prior studies that used a single outcome, separating the models for readmission and death resulted in better performance.

Badawi and colleagues'[34] models were the basis for the Philips eICU Discharge Readiness Score (DRS), which was later compared with other ICU severity of illness scores. The eRI database was used to develop a new cohort of 561,478 patients meeting inclusion criteria at 208 hospitals from 2013 to 2016. The DRS, APACHE-IV score, and Sequential Organ Failure Assessment (SOFA) score were calculated hourly from the fourth hour of ICU admission. The DRS showed higher discrimination for ICU mortality (AUROC, 0.942) than the APACHE-IV score (AUROC, 0.895) and the SOFA score (AUROC, 0.862). Some of the discrepancies were hypothesized to be partially related to increasing APACHE-IV and SOFA scores in those who survive caused by the inclusion of the worst value over the prior 24 hours, compared with DRS's inclusion of more recent values reflecting improvement in the clinical condition.

FUTURE TELEMEDICINE INTENSIVE CARE UNIT APPLICATIONS OF MACHINE LEARNING

The intersection of so-called big data and clinical decision support has provided an opportunity for advancements in the creation of and ability to generalize models. The existing tele-ICU clinical decision support models were generated using classic logistic regression techniques,[33] but novel ML algorithms are being developed from larger and richer data sets to address a wide variety of clinical dilemmas in critical care (**Table 1**).[35,36] External validation of these efforts using widely available data sets such as MIMIC-III[12] and eICU-CRD[13] will help guide the application of ML to the tele-ICU going forward.

Although predictive models are often a focus of research, any model predicting a rare outcome will have a low positive predictive value even if the discrimination is very high. An overlooked fact in designing and evaluating CDSS is that the target should only be the unrecognized prevalence of a condition rather than the total prevalence as the tool will only be useful in predicting what is not already known to the

Table 1
Recent studies of machine learning applicable to critical care

Sepsis	• Numerous studies evaluating a variety of ML methods to predict sepsis 3–12 h before onset[37–42] • Nonblinded randomized controlled trial of a proprietary ML algorithm (vs EMR severe sepsis alert) showed shorter ICU and hospital LOS and lower in-hospital mortality[43] • Retrospective study of ICU complications before and after implementation of real-time predictive analytics monitoring display associated with decrease in sepsis incidence[44] • Reinforcement learning model developed to assess optimal treatment of patients with septic shock (vasopressors vs IV fluids) predicted higher-value treatments than clinicians[45] • Switching-state autoregressive model predicted vasopressor administration and successful vasopressor weaning[46]
Mechanical Ventilation	• Random forest algorithm showed significant agreement with clinical experts in detecting ventilator asynchrony[51] • Multiple ML algorithms identified ventilator dyssynchrony, but the best-performing model differed by type of event[52] • Gradient-boosted decision trees algorithm predicted need for prolonged mechanical ventilation (AUROC, 0.820) and tracheostomy (AUROC, 0.830) at time of ICU admission[53] • Support vector machine algorithm trained using heart rate variability and patient-specific calibration data discriminated between light and deep sedation with 75% accuracy[54]
False-alarm Reduction	• Random forest model trained on human annotated alerts discriminated between true and false alarms for peripheral oximetry, blood pressure, and respiratory rate[55] • Multiple ML algorithms were used by teams competing to classify true and false arrhythmia alarms[56]
ICU Outcomes	• Gradient-boosting decision tree model developed using a single-center 14,962-patient cohort to predict the risk of ICU readmission was superior to other risk assessments (AUROC, 0.76 vs 0.58–0.65); validation in MIMIC-III had comparable results (AUROC, 0.71 vs 0.57–0.58)[57] • Random forest model developed using a single-center 6376-patient cohort to predict hospital-acquired pressure injury had an AUROC of 0.79 for stage 1 and stage 2+ injuries[58] • Recurrent neural network models developed using a single-center 9269-cardiac surgery patient cohort to predict mortality, renal replacement therapy, and postoperative bleeding requiring surgery outperformed other predictors in all outcomes (AUROCs of 0.95 vs 0.71, 0.96 vs 0.72, and 0.87 vs 0.53 respectively). Validation in MIMIC-III had comparable results[59] • Unstructured text data added to ML models from MIMIC-III improved prediction of death or prolonged ICU stay. Gradient-boosted machines slightly outperformed random forests, elastic net regression, and logistic regression[60] • Gradient-boosted decision tree model developed using a 53-center 237,173-patient ICU cohort predicted in-hospital mortality well (AUROC, 0.951 in training subset and 0.943 in validation subset)[61]

user.[27] One option to address this challenge is by diverting the low-yield but important screening activity to tele-ICU staff, allowing bedside staff to remain focused on their clinical activities. The following areas are some that the authors consider to be exciting and promising avenues potentially applicable in the tele-ICU.

Sepsis Prediction

Many ML algorithms to predict sepsis from clinical data have been developed:

- An elastic net logistic classifier applied to a single-center 1110-patient cohort to predict sepsis 4 hours before onset found that high-resolution vital signs combined with sociodemographic and clinical characteristics achieved an AUROC of 0.78.[37]
- Coupled hidden Markov models were compared with nonlinear support vector machine models applied to a single-center 1310-patient cohort from a MIMIC-III predecessor to predict septic shock during sepsis.[38]
- InSight, a proprietary ML model to predict sepsis 3 hours before onset developed from a MIMIC-III predecessor,[39] was then validated using the larger MIMIC-III cohort and found to outperform other assessments of sepsis (eg, SOFA scores) with an AUROC of 0.880 and to still perform well when tested with randomly missing data.[40]
- Deep learning models incorporating feedforward neural networks and long short-term memory to predict sepsis 3 hours before onset were derived using a 5803-patient cohort from a MIMIC-III predecessor and found to be capable of unsupervised feature extraction with improved performance compared with a proprietary regression model using hand-crafted features.[41]

More recently, ML approaches to sepsis detection have been validated in external data sets and real-world applications. Nemati and colleagues[42] developed a modified Weibull-Cox proportional hazards 65-feature model to predict sepsis 4 to 12 hours before onset using an internal 2-center 27,527-patient cohort with an AUROC of 0.83 to 0.85 and validated it using a 42,411-patient cohort from MIMIC-III with similar results (AUROC, 0.79–0.84). Using a larger data set than earlier models allowed prediction over significantly longer periods.

Shimabukuro and colleagues[43] performed the first randomized controlled trial of ML algorithms for sepsis detection in 2016. Although the InSight algorithm used 9 vital signs during its development,[39] the data requirements are flexible and had previously been evaluated using alternatives.[40] Shimabukuro and colleagues'[43] model included 6 features (age, blood pressure, heart rate, temperature, respiratory rate, and peripheral oxygen saturation) measured hourly in the 142 patients randomized during the 3-month study. Compared with a group monitored by the preexisting EMR severe sepsis alert system, the group monitored by the ML algorithm had significantly lower hospital LOS (10.3 days vs 13.0 days; $P = .042$), ICU LOS (6.31 days vs 8.40 days; $P = .030$), and in-hospital mortality (8.96% vs 21.3%; $P = .018$).[43] Note that caution must be taken in generalizing findings from a small, single-center, nonblinded trial; however, other studies have shown benefits from continuous real-time monitoring with multivariate predictive models for septic shock.[44]

Sepsis Management

Komorowski and colleagues[45] used a reinforcement learning agent to develop an artificial intelligence (AI) policy assessing whether vasopressors or intravenous (IV) fluids are the optimal intervention for a given patient with septic shock. The model was developed using a single-center 17,083-patient cohort from MIMIC-III, tested using a 128-center 79,073-patient cohort from the eRI database, and included 48 variables coded as a time-series over a 72-hour period around the estimated time of sepsis onset. A Markov decision process (MDP) modeled transitions between 750 discrete mutually exclusive patient states identified on cluster analysis. The theoretic optimum policy identified decisions (limited to actions taken by the clinician in the data set) that maximized rewards (ie, survival) for solving the MDP.

Bootstrapping evaluation of 500 candidate models and 500 clustering solutions on the MIMIC-III validation cohort provided the optimal model to be tested against the eRI database. The AI policy recommended higher vasopressor doses and lower IV fluid doses on average. Vasopressors were administered in 17% of eRI patients, whereas the AI policy recommended vasopressors in 30%. Mortality was shown to increase in a dose-dependent fashion as clinician intervention doses diverged from the AI policy recommendations.[45] An earlier study showed that a switching-state autoregressive model can predict vasopressor administration and weaning.[46]

Mechanical Ventilation

Lung protective ventilation decreases mortality in acute respiratory distress syndrome, and other causes of respiratory failure,[47,48] but the root cause of the difference is unclear.[49,50] The ability of modern mechanical ventilators to generate breath-to-breath pressure-volume curves offers unique opportunities to create rich high-bandwidth data sets. ML applied to a data set combining waveform and EMR data could detect factors affecting patient outcomes and optimize individual ventilator management.

A random forest model was able to discriminate between ventilator waveforms showing no asynchrony, delayed termination, and premature termination to a similar degree as clinical experts (kappa coefficients, 0.90, 0.90, and 0.91 respectively).[51] ML algorithms have also been applied to identify ventilator dyssynchrony from waveforms, and found to be effective at identifying double-triggered breaths, flow-limited breaths, and synchronous breaths, although the best model varied by dyssynchrony (AUROC, 0.89–0.95).[52]

TELEMEDICINE INTENSIVE CARE UNIT CLINICAL DECISION SUPPORT SYSTEM CONSIDERATIONS

There is abundant research on factors affecting bedside staff perception and acceptance of tele-ICU. Staff appreciate if tele-ICU provides improved workflow, improved monitoring, rapid availability, specialty expertise, and staff familiarity, but issues of unrealistic expectations and poor communication were barriers.[62–65] More recently Kahn and colleagues[66] found that tele-ICU systems perceived to be “appropriate, responsive, consistent, and integrated with bedside workflows” were associated with decreased mortality after being deployed. Tele-ICU CDSS must achieve these goals in addition to being autonomous, generalizable, transparent, coherent, and ideally educational; a black box is not an adequate decision aide.

These factors must be the foundation of tele-ICU ML CDSS development going forward. Tele-ICU nurses have been reported to care for 30 to 52 patients simultaneously,[67] with a median of 3 nurses per tele-ICU hub.[31] As the number of CDSS algorithms proliferate, they must be integrated into the tele-ICU workflow, which will differ significantly from the bedside because of the population-level surveillance taking place. Human factors engineering may be needed to ensure that CDSS that is effective at the bedside is not a burden in the tele-ICU.[30] CDSS deployment should be studied routinely using outcomes in both the short term (eg, best-practice adherence) and long term (eg, mortality). Furthermore, the constantly evolving state of the art in medicine requires rapid validation of CDSS models using large data sets as well as ongoing reevaluation and recalibration as circumstances change. Creating tele-ICU

ML CDSS will be challenging but has the potential to provide greater impact for more patients than any single-center CDSS.

SUMMARY

The use of ML in critical care CDSS is a rapidly developing field. The availability of large, comprehensive, granular data sets is fueling growth in ML algorithms that will be far more accurate and generalizable than in years past. The tele-ICU provides a framework to deploy ML algorithms at scale but will require emphasis on usability for monitoring large patient populations and studies of their effects on patient outcomes.

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