Harnessing the Power of Technology to Transform Delirium Severity Measurement in the ICU: Protocol for a Prospective Cohort Study

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Roshini Raghu[1] MBBS; Keivan Nalaie[1, 2] PhD; Ivan Ayala[1] MD; Juan Jose Morales Behaine[3, 4] MD; Juan Pablo Garcia-Mendez[2] MD; Hannah Friesen[1] BS; Kathleen Leistikow[1]; Anirban Bhattacharyya[5] MD; Arun Jayaraman[3, 4] MD; Pablo Moreno Franco[5, 6] MD; Alejandro Rabinstein[7] MD; Linda L Chlan[1] PhD; Malaz Boustani[8, 9] MD, MPH; Vitaly Herasevich[2] MD; Heidi Lindroth[8, 9, 10] PhD

[1]Division of Nursing Research Mayo Clinic Department of Nursing Rochester US
[2]Division of Critical Care Mayo Clinic Department of Anesthesiology and Perioperative Medicine Rochester US
[3]Department of Critical Care Medicine Mayo Clinic Phoenix US
[4]Department of Anesthesiology and Perioperative Medicine Mayo Clinic Phoenix US
[5]Department of Critical Care Medicine Mayo Clinic Jacksonville US
[6]Department of Transplantation Medicine Mayo Clinic Jacksonville US
[7]Department of Neurology Mayo Clinic Rochester US
[8]Center for Health Innovation and Implementation Science Indiana University School of Medicine Indianapolis US
[9]Center for Aging Research Regenstrief Institute School of Medicine Indianapolis US
[10]Division of Nursing Research, Department of Nursing Mayo Clinic Rochester US

Corresponding Author:
Heidi Lindroth PhD
Division of Nursing Research, Department of Nursing
Mayo Clinic
Rosa Parks Pavilion, 3rd Floor
Rochester
US

Abstract

Background: Delirium, an acute brain dysfunction, is a complication in up to 50% of intensive care unit (ICU) patients. Measuring and mitigating delirium severity can reduce associated morbidity and improve long-term health outcomes post-discharge. However, the
perceived complexity of the available delirium detection tools and clinical workload limits the routine assessment of delirium severity. Developing a passive digital marker for delirium severity combining routine electronic health record (EHR) and computer
vision technology data could be an implementable, scalable, and sustainable approach.

Objective: The primary objective is to develop a passive digital marker for delirium severity (PDM-DS) and examine its performance in comparison to validated delirium severity tools (aim 1 and 2). The secondary objective is to evaluate the acceptability and usability of the PDM-DS by patients, families, and clinicians (aim 3).

Methods: A prospective, longitudinal cohort study will be conducted to develop a PDM-DS using computer vision data and routinely collected EHR data. Following informed consent, the study team will collect image data through continuous digital video recordings of adult patients (>/= 50 years) in their ICU room, routine EHR data(demographic and clinical variables), and administer delirium severity assessments (4 x daily) until ICU discharge or death. The usability and acceptability of the developed PDM-DS will be evaluated by patients, families, and direct care clinicians in a pilot randomized controlled clinical trial (aim 3). Descriptive statistics (means, standard deviations, medians, interquartile ranges, frequencies) and statistical differences between study instruments will be examined. Convolutional neural networks and machine learning will inform model development, testing, and validation. Model performance statistics including accuracy, precision, recall, and the F1 score will be reported.

Results: Recruitment and data collection are ongoing. As of July 2024, 1,990 patients were screened (31% eligible, n=613), 306 approached (50%), and 71 participants were enrolled (23% enrollment rate). Among the 71 patients, the median age was 67 years (IQR 61-74), 65% male, and 93% Caucasian.

Conclusions: The PDM-DS could provide real-time, actionable feedback to direct care clinicians on the brain health of ICU patients. Early mitigation of delirium severity may decrease the risk of mortality, future Alzheimer's Disease and Related Dementia, and length of hospital stay. Clinical Trial: NCT06172491

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Original Paper

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Affiliations:

1. Division of Nursing Research, Department of Nursing, Mayo Clinic, Rochester.
2. Department of Anesthesiology and Perioperative Medicine, Division of Critical Care, Mayo Clinic, Rochester.
3. Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Arizona.
4. Department of Critical Care Medicine, Mayo Clinic, Arizona.
5. Department of Critical Care Medicine, Mayo Clinic, Florida.
6. Department of Transplantation Medicine, Mayo Clinic, Florida.
7. Department of Neurology, Mayo Clinic, Rochester.
8. Center for Health Innovation and Implementation Science, School of Medicine, Indiana University, Indianapolis, IN
9. Center for Aging Research, Regenstrief Institute, Indianapolis, IN

Corresponding Author:
Heidi Lindroth, Ph.D., R.N.
Principal Investigator
Mayo Clinic
200 First Street SW
Rochester, MN, USA
Lindroth.heidi@mayo.edu

Abstract

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Trial registration:
NCT06172491

Keywords: ICU Delirium, Computer Vision Technology, Passive digital marker, Delirium severity, Artificial Intelligence, Alzheimer's disease, and other Related Dementias

Introduction

Delirium, an acute brain dysfunction that manifests as a disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) accompanied by reduced awareness of the environment, is seen in up to 50% of mechanically ventilated patients in the intensive care unit (ICU).[1] Delirium increases the ICU and hospital length of stay, leading to an estimated annual cost of $152 billion U.S. dollars.[2-7] Furthermore, delirium occurrence has been associated with an increased risk of future Alzheimer's Disease and Related Dementia (ADRD), with 26% of delirium survivors developing cognitive scores closer to mild ADRD at a 12-month evaluation.[8] Previous studies report that not only the occurrence of delirium (presence/absence) but also its severity increases the risk of mortality, institutionalization, and ADRD.[3, 9-13] Delirium severity trajectories have been independently associated with increased 30-day mortality.[9] Increasing levels of delirium severity are also associated with decreased odds of discharge to home (multivariable; OR 0.78, 95%CI 0.71,0.86) and a faster rate of global cognitive decline in a postoperative population.[3, 10]

Despite the existence of validated tools for measuring delirium severity, it is not regularly measured in clinical care, and up to 70% of cases of delirium are missed in routine ICU care.[14-16] These gaps in clinical care could be attributed to clinician workload, staff turnover, and the perceived complexity or lack of knowledge on using current delirium monitoring tools.[17-21] Implementing frequent or continual documentation of minute-by-minute or hour-by-hour observations required for accurate delirium severity measurement is not feasible as it adds to the existing documentation burden faced by direct care clinicians.[21, 22] One solution to address these limitations is incorporating advanced Artificial Intelligence (AI) approaches such as Computer Vision Technology (CVT) in delirium care. CVT prospectively collects continuous observation (streaming) data that is collated and condensed for human decision-making.[23-27] Key features of delirium severity collected primarily through observation of the patient's behavior are prime candidates for continuous measurement by CVT, as outlined in **Figure 1.**

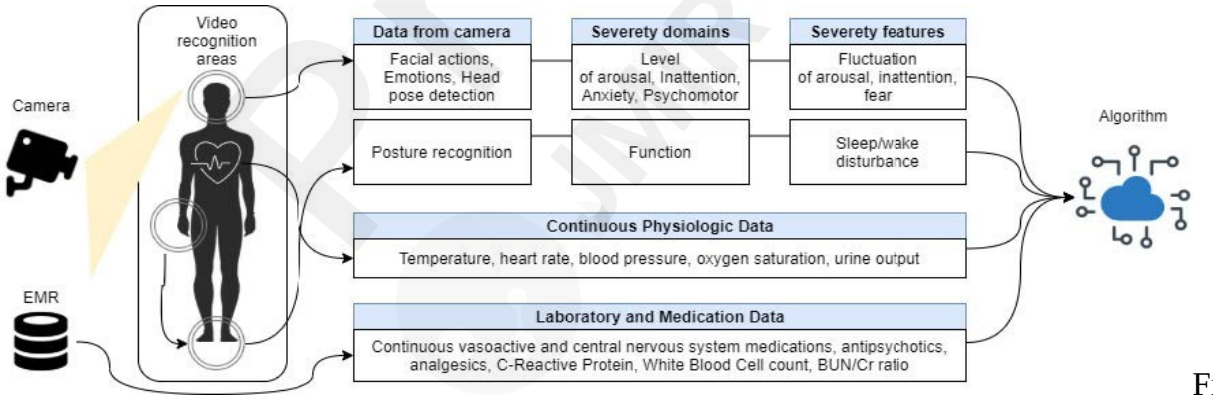


Figure 1: Mapping the outline of developing an AI algorithm through CVT and EHR data

Recent studies have demonstrated the feasibility of CVT use in the ICU, including delirium detection.[23, 24, 27-29] Compared to non-delirious patients (n=8), delirious patients (n=4) have demonstrated significantly different facial actions (e.g., lip, cheek, nose wrinkling), facial expressions (e.g., sadness, pain, fear, disgust), head pose/movement, and posture (e.g., lying, sitting, standing).[23] This pilot study provided foundational work to investigate further how continuous, non-contact CVT data can measure delirium severity in the ICU. While CVT data may be sufficient to capture some features of delirium severity, the algorithm's accuracy may improve with the addition of routinely collected EHR data such as medications and physiologic response (illness

severity). Therefore, we seek to address this gap in research and clinical care by developing a Passive Digital Marker for delirium severity (PDM-DS) that combines relevant CVT data with existing routine EHR data to produce a hybrid PDM that automatically and passively measures and monitors delirium severity.

Study Aims

1. To train convolutional neural networks (CNN) to measure delirium severity using prospective observational computer vision data in older adults (age ≥ 50 years) in the intensive care unit.
2. To develop a passive digital marker for delirium severity (PDM-DS) using prospectively collected computer vision data and/or routine Electronic Health Record data in a cohort of aging adult intensive care unit patients.
3. To determine the usability and acceptability of the passive digital marker for delirium severity in a prospective pilot randomized-controlled clinical trial in aging adult intensive care unit patients.

Methods

Study Design

This prospective longitudinal study is recruiting critically ill, aging adults (age ≥50 years) admitted to ICUs at the designated study sites. Institutional review board approval (IRB) has been obtained for aims 1-3 and is registered on clinicaltrials.gov (NCT06172491) by the principal investigator (H.L.). Agile methodologies are used by the study team to conduct the day-to-day operations of the study.

Informed consent

Informed consent for study participation is obtained from the patient or the identified proxy decision-maker, with the option to out at any time. Participants provide specific permissions to share patient health information including use of video images in future presentations, for use in future research, and with external collaborators. IRB approved study personnel approach eligible patients for inclusion into the study. Delirium status assessments are conducted prior to obtaining consent. If a potential patient is determined to have delirium, dementia, or a decreased level of arousal (RASS < -1 or > +1), proxy consent (i.e., legally authorized representative) is pursued.

Inclusion and Exclusion Criteria

Inclusion Criteria

For Aims 1-3, aging adults (age ≥ 50 years) with an estimated length of stay ≥24 hours in the ICU (including mechanically ventilated patients) and not admitted for acute alcohol intoxication, drug (prescribed or illicit) overdose, or withdrawal are eligible. For Aim 3, adult nurse clinicians (≥ 18 years), employed by the involved institutions, and assigned to care for a consented study patient for ≥4 hours are eligible. For Aim 3, adult proxy decision makers for patient participants (≥18 years) who are willing to complete the survey will be included.

Exclusion Criteria

For Aims 1-3, patients admitted for acute alcohol intoxication, drug (prescribed or illicit) overdose or withdrawal, acute neural injury and unable to communicate with research team due to sensory deficits (aphasic, blind, deaf) or language (requires interpreter) will be excluded. For Aim 3, nurse clinicians not assigned to the study participant and proxy decision makers who did not visit the patient in the ICU during the study period will be excluded.

Instruments & Data Collection

For Aims 1 and 2 (observational, n~400), longitudinal data collection includes continuous digital video recordings of the patient in their ICU room, routine EHR data, and delirium severity assessments collected by the study team. For Aim 3, data will be collected using the System Usability Scale (SUS), Mayo Clinic Acceptability survey, and the Treatment Acceptability and Preferences (TAP) questionnaire. Data will be collected from enrollment until death and/or discharge from the ICU.

CVT Data

High-resolution and wide field-of-view computer vision data are collected 24/7 through video cameras for a minimum of 72 hours or until discharge or death, whichever occurs first. Cameras directly face the patient's bed (foot of bed, both sides of bed). A touchscreen user-friendly interface allows clinical staff, families, or patients to stop/restart recording. The observational data collected through video recordings will be used to perform face detection, facial expression, head pose detection, posture recognition, vital sign waveform data, and disturbance in the sleep-wake cycle as outlined in Table 1.

Table 1. Computer vision data (images) collected through continuous video recordings.

	Description of Proposed Analysis of Computer Vision data
Face detection	FaceNet algorithm, Inception-ResNet V1 model. Accuracy Threshold: ≥0.90. This is a publicly available open-source code developed by Google.[30] Foundation to all other measurements
Facial Action Unit (FAU)	OpenFace deep neural network 2.2.0 toolbox to detect FAUs (n~AUs).[31] Accuracy Threshold: ≥70% identified. Includes eyebrows (upper, lower, blink), lip movement. Coded as present (yes/no) and graded in intensity (0-5). Open-source, publicly available code.
Facial expression	Facial Action Coding System with OpenFace deep neural network 2.2.0 toolbox.[31] Eight common facial expressions/emotions. Frequency and length calculated. Anger, contempt, disgust, fear, happiness, pain, sadness, and surprise
Head pose detection	OpenFace deep neural network 2.2.0 toolbox.[31] Detects movement, position of head (rotation, up/down movements, side to side).
Eye/Gaze Tracking	OpenFace deep neural network 2.2.0 toolbox.[32]
Posture recognition	

	OpenPose multi-person estimation model.[33] Localizes anatomical key-points of limbs/joints, length of limbs/angles inform recognition of movements and activity. Will calculate speed and absence of movement (including presence of chemical or physical restraints). Accuracy Threshold: ≥70%. Open-source, publicly available code.
Sleep-wake cycle	Posture recognition will measure patient posture, movement, and sleep poses.
Acute Onset/fluctuation	Acute onset will be defined as an abrupt change in any of the CVT features. Fluctuation will be defined as the % variation in any of the CVT features.
Cameras	Each ICU room will begin with 1-3 video cameras to investigate which camera positions/angles are necessary to capture the outlined information. The necessity of >1 camera will be continually reviewed.

Electronic Health Record Data

Patient demographic and clinical variables pertaining to the current ICU stay will be extracted from the electronic health record. Table 2 outlines these data. The variables selected for inclusion are informed by literature[34-36]. EHR data is automatically extracted every 15 minutes and stored in the ICU DataMart for all Mayo Clinic locations.[37] For the Delirium Severity feature, we will extract the RASS score and sedation administration to assess for the fluctuating course and medication administration to assess for psychomotor disturbance. [38]

Table 2. Routine EHR data to inform PDM-DS for delirium severity.

	Data Collected
Illness Severity	Vital sign (min, max, range) Vasopressor use Anti-infective use SOFA score
Delirium Severity	RASS score (min, max, range) Propofol use Dexmedetomidine use Benzodiazepine use Opioid use Paralytics use Benzodiazepine use Antidepressant use Sleep enhancement (e.g. melatonin)

	Antiseizure use Neurological assessment scales
Co-variates	Age Sex Ethnicity Race Past Medical History

Abbreviations: RASS = Richmond Agitation and Sedation Scale; SOFA= Sequential Organ Failure Assessment Score

Standardized Delirium Severity Measurement

The principal investigator (H.L.) trained the study team members to administer standardized, validated delirium severity assessments outlined in Table 3**,** four times daily between the hours of 0500- 2200 until death and/or discharge from the ICU. Observational field study accompanies tool administration and uses a standardized data collection form to promote inter-rater reliability. Observations include behaviors, emotions, head, eye, and limb movement, or the absence of these items. The study team timestamps the CVT data images when assessments are performed to assist with labeling and annotation. Concurrent to delirium severity assessments, the study team asks the assigned direct care nurse their level of concern for the patient's condition using the Worry Factor Score.

Table 3. Delirium and delirium severity assessment administered 4xdaily between 0500-2200

Tool	Definition/Concept
CAM-ICU[39, 40]	Gold Standard. Scored as positive/negative. Sens: 85% Spec: 87%
ICDSC[41, 42]	Validated ICU tool. Score (0-8) on symptom presence. Sens: 95%, Spec: 91%
CAM-ICU-7[41, 43]	Validated delirium severity tool scored directly from CAM-ICU, Cronbach α=0.85. Scoring (0-7): 0-2=no delirium, 3-5=mild/moderate delirium, 6-7=severe delirium.
DRS-R-98[**4**4, 45] (non-intubated only)	Validated delirium severity tool for non-intubated patients.16-item (0-44 score) symptom/feature measurement. Cronbach α=0.90

The PMD study (PI: Boustani) and the BASIL study findings guided the selection of these tools.[43, 44, 46, 47] Scales, and sub-components of each scale, will be applied as a continuum of delirium severity to train the CVT neural networks.

Abbreviations: CAM-ICU=Confusion Assessment Method for ICU; DRS-R-98=Delirium Rating Scale-R-98; ICDSC= Intensive Care Delirium Screening Checklist

For Aim 3 (pilot RCT, n=30), we will enroll one patient at a time across ICUs with similar

patient populations and delirium rates to reduce the risk of contamination and randomize (1:1, computer-generated assignment) to usual care (nurse administered CAM-ICU, standard care plan in place) or intervention (PDM-DS score, suggested interventions for level of severity, e.g., mild = reorientation). The patient, proxy decision maker, and direct care clinicians assigned to care for patient will complete acceptability and usability assessments: System Usability Scale (SUS), Mayo Clinic Acceptability survey, and the Treatment Acceptability and Preferences (TAP) questionnaire. Table 4 outlines data collection for aim 3.

Table 4 – Usability and Acceptability of PDM-DS

Tool	Description	Participant, Time of Completion
System Usability Scale (SUS)[48]		
	10 questions rate usability on a 1-5 scale, strongly disagree-strongly agree	Nurse clinician, end of shift with study patient
Mayo Clinic Acceptance Survey[28]		
	10 questions on use of computer vision technology in ICU, Likert scale 1-5	Nurse clinician, end of shift with study patient
Treatment Acceptability and Preferences Questionnaire (TAPQ)[49]		
	4 questions, Likert scale on effectiveness, believability, and acceptability of PDM-DS, high internal consistency (alpha≥0.80)	Patient and identified proxy, at ICU discharge
EHR Data		
	Compliance with A2F bundle[50], time to extubation, ICU mortality	Extracted from EHR at ICU discharge, Secondary outcomes

Usual Care Group: Nurse administration of the CAM-ICU delirium assessment once every 12 hours and the administration of evidence-based strategies to mitigate delirium such as the A2F bundle (i.e., usual care).

Intervention Group: The PDM-DS score will be displayed on a monitor in the patient's ICU room for the nurses (formal caregiver) reference. Evidence-based strategies to mitigate delirium severity, such as the A2F bundle, will be suggested underneath the score for the nurse clinician to apply. Nurses will be asked to provide feedback on if they felt the intervention suggested was appropriate. These are the initial steps to develop a decision-support tool for the nurse to mitigate delirium severity.

Statistical Analysis

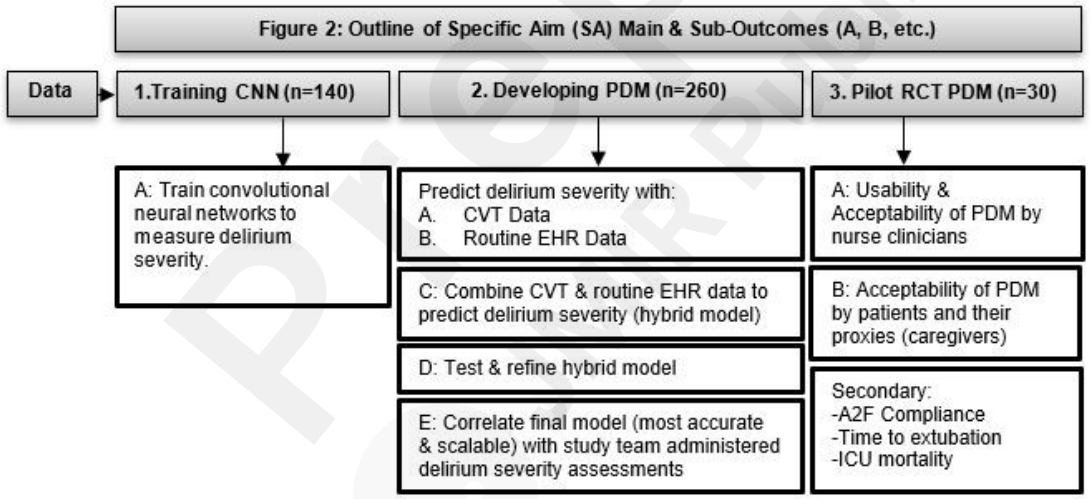
Power

The proposed sample size was calculated per aim and assumes a delirium rate (prevalence, incidence) of 45% in enrolled patients as reported in recent literature.[51, 52] Dr. Lindroth recognizes the likelihood that this study may be underpowered. Findings will inform future grant applications to adequately power study aims. Aim 1) The minimum computer vision frames (2,000) needed per class label (200 estimated labels; 80 CVT features, 120 delirium severity observations) was used to calculate the sample size.[23] Assuming an average of 2 frames/second, and an average 48-hours of video recording per patient, ~140 patients will be needed to inform aim 1. Aim 2) An additional ~260 patients will be recruited to inform aim 2 for a total sample of 400. This is powered for a confidence level of 0.95, an interval width of 0.10, and the ability to detect a 0.80 area under the curve. Aim 3) An additional 30 patients will be recruited for the pilot RCT. Effect sizes will power future R01 or R-series grant applications designed to further test and refine the PDM-DS.

Data Analysis

Descriptive statistics (means, standard deviations, medians, interquartile ranges, frequencies) will be reported. Data among sites will be examined for statistical differences. Modeling assumptions (dependent on types-of models used) will be verified.[23, 27, 29, 53] Missing data will be examined for level of missingness (Missing Completely at Random, Missing at Random, etc.) and procedures such as multiple imputation completed as needed. **Figure 2** provides an overview of planned statistical analysis.

Outline of Specific Aim (SA) Main & Sub-outcomes (A, B, etc.)



Aim 1. Data will be split randomly 80/20 for training and testing purposes. Labeling and annotation of the CV images to train the CNNs will follow a stepwise process. Active learning is being used to minimize the number of manual annotations needed for modeling procedures. Classification accuracy, model performance data, correlations between the final CNN model and administered delirium severity assessments, will be evaluated, and reported.

Aim 2. Exploratory analysis, factor association measurement, and multi-class machine learning (ML) models and ensembles (e.g., random forests, gradient boosting, bagging methods, and support vector machines) will inform analysis. Depending on the number of delirium severity classes (*i.e.* mild, moderate, severe) identified, classification probabilities will be calculated. Classification to one of the severity classes will be based on class with highest predicted probability. Test error, variance,

entropy, inference FLOPS, number of trees, and depth of forest statistics will inform model selection. Accuracy and precision of classification will evaluate model performance. Nested cross-validation will evaluate the final model(s), perform hyperparameter searches, and estimate generalization error of the underlying model(s). Performance statistics (i.e., sensitivity, specificity) will be reported. The Youden Index will determine optimal cut-off points for mild, moderate, and severe delirium.[54] ICU outcomes (admission and discharge time, mortality, discharge disposition, 30-day readmission) associated with the models will be reported for internal validation. We will select the model that balances accuracy with scalability for future testing and evaluation.

Aim 3. We will calculate means, standard deviations, and 90% confidence intervals for the System Usability Scale (SUS), Mayo Clinic Acceptability survey, and the Treatment Acceptability and Preferences (TAP) questionnaire. We hypothesize that the PDM-DS will be acceptable and usable by frontline ICU nurse clinicians, patients, and identified proxies. The secondary outcomes of A2F bundle compliance, time to extubation, and ICU mortality will be collected and compared between groups. [50] Generated effect sizes will power future R01 grant applications.

Results

As of January 2023, data collection has begun across three healthcare institution sites, and the process of protocol adoption has started in a 4th site. We have screened 1,990 patients, approached 306, and enrolled 71 participants as of July 2024 as listed on Table 5.

Table 5. Data collected as of July 2024.

Screened	Approached	Enrolled	Number of images collected	Number of delirium severity assessments completed
1,900	306	71	>25,000,000	>600

The primary reason patients declined participation in the study was feeling uncomfortable with the continuous recordings and the video camera. Secondary reasons to decline study participation included patients not being interested in research while in the ICU and finding the study team assessments (4 times daily delirium assessments) exhausting. To address these limitations to study recruitment, the principal investigator has presented to formal community groups and the study's data safety monitoring board to gain insight into how to improve the study. As a result, the study team is moving the camera to a different location in the room and has developed a frequently asked questions flyer for patients and family to reference.

The main inclusion criteria that were not met, leading to ineligible patients, was a length of stay of 24 hours or greater in the ICU (29.4%) followed by acute neurological injury (11.1%). Additional reasons for slower recruitment than expected are equipment malfunctions and availability, study team vacancies, and length of onboarding to study protocol.

Discussion

Delirium, while currently categorized as present or absent, lacks granularity in assessing severity.[55] While this is sufficient for detection and diagnosis, it may be better to obtain information on the level or trajectory of delirium severity. The passive digital marker for delirium severity (PDM-DS) aims to address this limitation and provide immediate and actionable information

to healthcare clinicians on the patient's brain health, similar to other vital signs like heart rate. As clinicians work to mitigate delirium severity, the PDM-DS would provide actionable and nonjudgmental feedback on the interventions' effectiveness, providing the opportunity to individualize care based on the patient's response. The underlying hypothesis of this work is that clinicians will take more action to mitigate delirium severity if they receive prompt and actionable feedback on the performance of their interventions in real time. This study presents a novel approach to measuring delirium severity through the development of a scalable, feasible, and passive digital marker.

Early recognition and mitigation of severity play a crucial role in preventing adverse health outcomes and enhancing the lives of critically ill adults. The proposed PDM-DS may improve the lives of ICU patients by providing timely and actionable feedback to bedside clinicians about delirium severity, supporting the mitigation of delirium severity. In turn, the risk of future mortality and morbidities, including Alzheimer's Disease and Related Dementias (ADRD), associated with delirium severity may be reduced. .[8] The close association between delirium and dementia has been studied exclusively, with a possible synergistic interrelationship between the two conditions. [56-58] Hospitalized ADRD patients are at least twice as likely to develop delirium superimposed on dementia (DSD) and patients who develop in-hospital delirium are at a higher risk to subsequently develop dementia in the future. A prospective study on hospitalized ADRD patients reported 33% had delirium superimposed on delirium and 25% of those patients with DSD had increased mortality rate, functional decline, and increased hospital length of stay.[59] Delirium superimposed on dementia can be challenging to detect in the clinical setting due to the overlapping cognitive and behavioral features between dementia and delirium.[60] Yet, it is critical to detect delirium in this population as it likely signifies a medical emergency. We aim for our PDM-DS to be a valuable tool to improve the early recognition of delirium superimposed on dementia. Future studies may also examine how computer vision could aid in recognition of symptoms such as pain and anxiety in ADRD patients. Focusing on this vulnerable patient population may help reduce their inpatient and posthospitalization morbidity and mortality and improve their quality of life.

Clinical research to identify delirium subtypes and biological biomarkers could be accelerated with the use of a passive digital marker for delirium severity (PDM-DS). Instead of relying on inconsistent clinical assessments, or resource intensive research assessments, the PDM-DS would provide continuous monitoring and real time measurement across a large population of critically ill patients. The availability of such data could greatly expand and expedite the use of data science methods such as machine learning, elucidating biological and clinically relevant relationships that, in turn, could improve clinical trials aimed at identifying effective treatments for delirium. Furthermore, the PDM-DS can be used to study the trajectories of delirium severity, and identify clinical interventions to modify the trajectory in real time, therefore potentially mitigating adverse outcomes such as Post Intensive Care Syndrome.[9]

The ICU of the future is poised to harness advanced AI technologies and ambient monitoring, specifically Computer Vision Technology (CVT), to augment patient monitoring, assessment, and support clinical decision-making. Recent studies show that CVT collected through ambient sensors in the ICU can perform autonomous patient monitoring, quantify progress in patients' mobility, monitor safety compliance, and detect differences between delirious and non-delirious patients.[23-25, 27, 28, 32, 61] This type of ambient CVT operates at a low variable cost, is passive, fatigue-free, and ceaseless, thus ideal for continuously measuring delirium severity. Depending on the performance of CVT to automatically measure delirium severity, additional ambient sensors may be considered in future studies to improve model performance and/or develop a more scalable and sustainable passive digital marker. These ambient sensors include passive infrared motion sensors,

bed sensor devices that measure sleep quality, ambient vital sign monitors that measure continuous heart rate and respiratory rate and thermography are a few examples that could be used to automatically measure delirium severity and provide feedback for delirium mitigation strategies.[62]

Limitations

The critical care setting presents unique challenges to autonomous delirium severity measurement, including paralyzed, mechanically ventilated, deeply sedated patients and the use of physical or chemical restraints. The impact of sedation levels on facial actions and expressions remains insufficiently documented. Therefore, the study team will closely document the level of sedation and the use of restraints in study participants to investigate this further.

It has been noted that privacy concerns play a significant role in limiting recruitment to our study. Since recruitment began, the study team stated that the most common reason for denied participation to the study is because the patients/families do not want to be recorded, followed by the discomfort in taking part in research while at the ICU. To address this issue, Dr. Lindroth met with the Health Data and Technology Advisory (DaTA) Board, where the first author (R.R.) presented a mock consent and received feedback on the approach towards the consenting process. Study investigators (H.L. and V.H.) are also meeting with the ICU healthcare teams and patient partners to address these concerns and will continue to do so throughout the proposed project. In terms of analyzing computer vision data, we have identified that collection of minimal amounts of information needed to train and use the model so that patients' privacy and safety are protected. This includes blurring or removing unnecessary pieces of data that do not contribute to model development. To address staff concerns with the use of computer vision technology, the PI and study team presented to unit meetings, held lunch and learn events, and recruited nurse champions from each participating unit to proactively learn and address privacy concerns. These efforts continue as the work is ongoing.

We have also encountered unforeseen challenges in the labeling and training of computer vision data that hinder progress. To optimize data collection through camera placement, the study team frequently uses the ICU simulation center to conduct experiments on camera placement, angle, aperture, and lighting.

This study is the first study to our knowledge that aims at creating a PDM-DS for continuous delirium severity measurement. Our study proposes a solution to the identification of missed delirium cases in critical care practice so that patients receive early interventions for delirium mitigation. As our assessments also encompass delirium severity, patients with severe/moderate delirium can be identified early and specific behavior related to these severities can be studied in detail. Our study aims to leverage the foundational work completed Dr. Herasevich's laboratory to substantiate previous findings and generate new findings using CVT.[26, 28, 37] The results of the proposed study will be reported in full transparency and data shared when applicable. The relevant biological variables of assigned sex and age will be used as covariates.

Conclusion

This study aims to develop a passive digital marker for delirium severity using computer vision technology (CVT), a form of artificial intelligence, combined with routine electronic health record data. By combining two different data modalities enhanced with AI we anticipate significant clinical impact. The continuous measurement of delirium severity, akin to a vital sign, is expected to

prompt clinicians to take early and frequent actions for delirium mitigation. Through early recognition and mitigation of delirium severity, the proposed PDM-DS may decrease the risk of an extended hospital length of stay, Alzheimer's Disease and Related Dementias, mortality, and improve the quality of life of ICU patient survivors and families.

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Conflicts of Interest

H.L. and the reported work are supported by a National Institute of Health, National Institute on Aging K23 AG076662-03 award. Pending intellectual property disclosures for H.L., K.N., V.H.

Abbreviations

AI: Artificial intelligence
AU: Action Unit
ADRD: Alzheimer's Disease and Other Related Dementia
BASIL: Better Assessment of Illness
CAM-ICU: Confusion Assessment Method for ICU
CNN: Convolutional Neural Network
CV: Computer Vision
CVT: Computer Vision Technology
DRS-R-98: Delirium Rating Scale-R-98
EMR: Electronic Health Record
FAU: Facial Action Unit
ICDSC: Intensive Care Delirium Screening Checklist
ICU: Intensive Care Unit
IRB: Institutional Review Board
JMIR: Journal of Medical Internet Research
ML: Machine Learning
PDM-DS: Passive Digital Marker for Delirium Severity
RCT: Randomized Control Trial
TAPD: Treatment Acceptability and Preferences Questionnaire
SUS: System Usability Scale

Multimedia Appendix 1

References

1. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5-TR)*. Vol. Fifth Edition. 2022: American Psychiatric Association.
2. Ha, A., et al. *A contemporary population-based analysis of the incidence, cost, and outcomes of postoperative delirium following major urologic cancer surgeries*. in *Urologic Oncology: Seminars and Original Investigations*. 2018. Elsevier.
3. Khan, B.A., et al., *The CAM-ICU-7 delirium severity scale: A novel delirium severity instrument for use in the intensive care unit.* Critical care medicine, 2017. **45**(5): p. 851.
4. Gleason, L.J., et al., *Effect of delirium and other major complications on outcomes after elective surgery in older adults.* JAMA surgery, 2015. **150**(12): p. 1134-1140.
5. Vasilevskis, E.E., et al., *The cost of ICU delirium and coma in the intensive care unit patient.* Medical care, 2018. **56**(10): p. 890.
6. Leslie, D.L., et al., *One-year health care costs associated with delirium in the elderly population.* Archives of internal medicine, 2008. **168**(1): p. 27-32.
7. Leslie, D.L. and S.K. Inouye, *The importance of delirium: economic and societal costs.* Journal of the American Geriatrics Society, 2011. **59**: p. S241-S243.
8. Pandharipande, P.P., et al., *Long-term cognitive impairment after critical illness.* New England Journal of Medicine, 2013. **369**(14): p. 1306-1316.
9. Lindroth, H., et al., *Delirium severity trajectories and outcomes in ICU patients. Defining a dynamic symptom phenotype.* Annals of the American Thoracic Society, 2020. **17**(9): p. 1094-1103.
10. Vasunilashorn, S.M., et al., *Delirium severity post-surgery and its relationship with long-term cognitive decline in a cohort of patients without dementia.* Journal of Alzheimer's Disease, 2018. **61**(1): p. 347-358.
11. Andrews, P.S., et al., *Relationship between intensive care unit delirium severity and 2-year mortality and health care utilization.* American Journal of Critical Care, 2020. **29**(4): p. 311-317.
12. Rosgen, B.K., et al., *The association of delirium severity with patient and health system outcomes in hospitalised patients: a systematic review.* Age and ageing, 2020. **49**(4): p. 549-557.
13. Girard, T.D., et al., *Clinical phenotypes of delirium during critical illness and severity of subsequent long-term cognitive impairment: a prospective cohort study.* The Lancet Respiratory Medicine, 2018. **6**(3): p. 213-222.
14. Steis, M.R. and D.M. Fick, *Are nurses recognizing delirium? A systematic review.* Journal of gerontological nursing, 2008. **34**(9): p. 40-48.
15. Spronk, P.E., et al., *Occurrence of delirium is severely underestimated in the ICU during daily care.* Intensive Care Med, 2009. **35**(7): p. 1276-80.
16. Pisani, M.A., J.W. Devlin, and Y. Skrobik, *Pain and Delirium in Critical Illness: An Exploration of Key 2018 SCCM PADIS Guideline Evidence Gaps.* Semin Respir Crit Care Med, 2019. **40**(5): p. 604-613.
17. Pisani, M.A., J.W. Devlin, and Y. Skrobik. *Pain and delirium in critical illness: An exploration of key 2018 SCCM PADIS guideline evidence gaps*. in *Seminars in respiratory and critical care medicine*. 2019. Thieme Medical Publishers.
18. Devlin, J.W., et al., *Assessment of delirium in the intensive care unit: nursing practices and perceptions.* American Journal of Critical Care, 2008. **17**(6): p. 555-565.
19. Devlin, J.W., et al., *Current perceptions and practices surrounding the recognition and treatment of delirium in the intensive care unit: a survey of 250 critical care pharmacists from eight states.* Annals of Pharmacotherapy, 2011. **45**(10): p. 1217-1229.

20. Oxenboll-Collet, M., et al., *Nurses' and physicians' perceptions of Confusion Assessment Method for the intensive care unit for delirium detection: focus group study.* Nurs Crit Care, 2018. **23**(1): p. 16-22.
21. Rowley-Conwy, G., *Barriers to delirium assessment in the intensive care unit: A literature review.* Intensive and Critical Care Nursing, 2018. **44**: p. 99-104.
22. Collins, S., et al. *Quantifying and visualizing nursing flowsheet documentation burden in acute and critical care*. in *AMIA Annual Symposium Proceedings*. 2018. American Medical Informatics Association.
23. Davoudi, A., et al., *Intelligent ICU for autonomous patient monitoring using pervasive sensing and deep learning.* Scientific reports, 2019. **9**(1): p. 8020.
24. Greco, M., P.F. Caruso, and M. Cecconi. *Artificial intelligence in the intensive care unit*. in *Seminars in Respiratory and Critical Care Medicine*. 2020. Thieme Medical Publishers, Inc. 333 Seventh Avenue, 18th Floor, New York, NY ….
25. Milstein, A. and E.J. Topol, *Computer vision's potential to improve health care.* The Lancet, 2020. **395**(10236): p. 1537.
26. Pickering, B.W., et al., *Clinical review: the hospital of the future-building intelligent environments to facilitate safe and effective acute care delivery.* Critical care, 2012. **16**: p. 1-11.
27. Yeung, S., et al., *A computer vision system for deep learning-based detection of patient mobilization activities in the ICU.* NPJ digital medicine, 2019. **2**(1): p. 11.
28. Glancova, A., et al., *Are we ready for video recognition and computer vision in the intensive care unit? A survey.* Applied clinical informatics, 2021. **12**(01): p. 120-132.
29. Magi, N. and B. Prasad, *Activity monitoring for ICU patients using deep learning and image processing.* SN Computer Science, 2020. **1**: p. 1-8.
30. Cahyono, F., W. Wirawan, and R.F. Rachmadi. *Face recognition system using facenet algorithm for employee presence*. in *2020 4th international conference on vocational education and training (ICOVET)*. 2020. IEEE.
31. Baltrusaitis, T., et al. *Openface 2.0: Facial behavior analysis toolkit*. in *2018 13th IEEE international conference on automatic face & gesture recognition (FG 2018)*. 2018. IEEE.
32. Wood, E., et al. *Rendering of eyes for eye-shape registration and gaze estimation*. in *Proceedings of the IEEE international conference on computer vision*. 2015.
33. Cao, Z., et al., *OpenPose: Realtime Multi-Person 2D Pose Estimation Using Part Affinity Fields.* IEEE Trans Pattern Anal Mach Intell, 2021. **43**(1): p. 172-186.
34. Halladay, C.W., A.Y. Sillner, and J.L. Rudolph, *Performance of electronic prediction rules for prevalent delirium at hospital admission.* JAMA network open, 2018. **1**(4): p. e181405-e181405.
35. Corradi, J.P., et al., *Prediction of incident delirium using a random forest classifier.* Journal of medical systems, 2018. **42**: p. 1-10.
36. Coombes, C.E., K.R. Coombes, and N. Fareed, *A novel model to label delirium in an intensive care unit from clinician actions.* BMC medical informatics and decision making, 2021. **21**(1): p. 1-12.
37. Herasevich, V., et al., *ICU data mart: a non-iT approach. A team of clinicians, researchers and informatics personnel at the Mayo Clinic have taken a homegrown approach to building an ICU data mart.* Healthcare informatics: the business magazine for information and communication systems, 2011. **28**(11): p. 42-45.
38. Jones, A.E., S. Trzeciak, and J.A. Kline, *The Sequential Organ Failure Assessment score for predicting outcome in patients with severe sepsis and evidence of hypoperfusion at the time of emergency department presentation.* Critical care medicine, 2009. **37**(5): p. 1649.
39. Ely, E.W., et al., *Evaluation of delirium in critically ill patients: validation of the Confusion*

Assessment Method for the Intensive Care Unit (CAM-ICU). Critical Care Medicine, 2001. **29**(7): p. 1370-1379.
40. Ely, E.W., *Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU).* JAMA, 2001. **286**.
41. Krewulak, K.D., et al., *The CAM-ICU-7 and ICDSC as measures of delirium severity in critically ill adult patients.* PLoS One, 2020. **15**(11): p. e0242378.
42. Ho, M.H., et al., *Diagnostic Performance of Delirium Assessment Tools in Critically Ill Patients: A Systematic Review and Meta-Analysis.* Worldviews Evid Based Nurs, 2020. **17**(4): p. 301-310.
43. Khan, B.A., et al., *The Confusion Assessment Method for the ICU-7 Delirium Severity Scale: A Novel Delirium Severity Instrument for Use in the ICU.* Critical Care Medicine, 2017. **45**(5): p. 851-857.
44. Jones, R.N., et al., *Assessment of Instruments for Measurement of Delirium Severity: A Systematic Review.* JAMA Intern Medicine, 2018.
45. Trzepacz, P.T., et al., *Validation of the Delirium Rating Scale-revised-98: comparison with the delirium rating scale and the cognitive test for delirium.* J Neuropsychiatry Clin Neurosci, 2001. **13**(2): p. 229-42.
46. Khan, B.A., et al., *Pharmacological Management of Delirium in the Intensive Care Unit: A Randomized Pragmatic Clinical Trial.* J Am Geriatr Soc, 2019. **67**(5): p. 1057-1065.
47. Vasunilashorn, S.M., et al., *New Delirium Severity Indicators: Generation and Internal Validation in the Better Assessment of Illness (BASIL) Study.* Dement Geriatr Cogn Disord, 2020. **49**(1): p. 77-90.
48. Lewis, J.R., *The system usability scale: past, present, and future.* International Journal of Human–Computer Interaction, 2018. **34**(7): p. 577-590.
49. Sidani, S., et al., *Assessment of preferences for treatment: validation of a measure.* Research in nursing & health, 2009. **32**(4): p. 419-431.
50. Pun, B.T., et al., *Caring for critically ill patients with the ABCDEF bundle: results of the ICU liberation collaborative in over 15,000 adults.* Critical care medicine, 2019. **47**(1): p. 3.
51. Stollings, J.L., et al., *Delirium in critical illness: clinical manifestations, outcomes, and management.* Intensive care medicine, 2021. **47**(10): p. 1089-1103.
52. Girard, T.D., et al., *Haloperidol and ziprasidone for treatment of delirium in critical illness.* New England Journal of Medicine, 2018. **379**(26): p. 2506-2516.
53. Shinde, S., A. Kothari, and V. Gupta, *YOLO based human action recognition and localization.* Procedia computer science, 2018. **133**: p. 831-838.
54. Ruopp, M.D., et al., *Youden Index and optimal cut-point estimated from observations affected by a lower limit of detection.* Biometrical Journal: Journal of Mathematical Methods in Biosciences, 2008. **50**(3): p. 419-430.
55. Miranda, F., et al., *Confusion Assessment Method for the intensive care unit (CAM-ICU) for the diagnosis of delirium in adults in critical care settings.* The Cochrane Database of Systematic Reviews, 2018. **2018**(9).
56. Fong, T.G. and S.K. Inouye, *The inter-relationship between delirium and dementia: the importance of delirium prevention.* Nature Reviews Neurology, 2022. **18**(10): p. 579-596.
57. Fong, T.G., et al., *The interface between delirium and dementia in elderly adults.* The Lancet Neurology, 2015. **14**(8): p. 823-832.
58. Gross, A.L., et al., *Delirium and long-term cognitive trajectory among persons with dementia.* Archives of internal medicine, 2012. **172**(17): p. 1324-1331.
59. Fick, D.M., et al., *Delirium superimposed on dementia is associated with prolonged length of stay and poor outcomes in hospitalized older adults.* Journal of hospital medicine, 2013. **8**(9): p. 500-505.

60. Nitchingham, A. and G.A. Caplan, *Current challenges in the recognition and management of delirium superimposed on dementia.* Neuropsychiatric Disease and Treatment, 2021: p. 1341-1352.
61. Yeung, S., et al., *Bedside computer vision-moving artificial intelligence from driver assistance to patient safety.* N Engl J Med, 2018. **378**(14): p. 1271-1273.
62. Saner, H., et al., *Potential of ambient sensor systems for early detection of health problems in older adults.* Frontiers in cardiovascular medicine, 2020. **7**: p. 110.