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Original Research

Association of Medication Exposures in Critically Ill Patients with Post-Intensive Care Syndrome (PICS)

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Background

Post-intensive care syndrome (PICS) is a new or worsening neuropsychological and functional disability that develops in intensive care unit (ICU) survivors after a prolonged ICU stay and persists beyond discharge from the hospital. Risk factors include immobility, delirium, agitation, mechanical ventilation, physical restraints, acute respiratory distress syndrome (ARDS), sepsis, and multisystem failure. Many patients with these conditions receive prolonged sedation, neuromuscular blockade, and systemic glucocorticoids which could potentially provide modifiable medication risk factors of PICS. Therefore, this study sought to explore the association of medication exposure in the ICU and symptoms of post-intensive care syndrome (PICS).

Methods

Single-center, retrospective study of adult ICU patients, between April 2020 through July 2023 enrolled in the institution's Critical Illness Recovery Program after discharge. PICS symptoms were evaluated using standardized screening tools and physician identification of psychological, cognitive, and physical PICS collected from electronic health record documentation. Medications evaluated included opioids, benzodiazepines, propofol, dexmedetomidine, vasopressors, neuromuscular blockers, inhaled epoprostenol, corticosteroids, antihistamines, blood products, antibiotics, antidepressants, and antipsychotics. Associations with PICS symptoms were analyzed using regression partial correlations. Correlates of PICS whose relationship exceeded a clinically relevant threshold ($r \geqslant \pm .20$) were identified. Partial correlations were then computed, controlling for other predictors of PICS, to identify possible best medication associations of PICS.

Results

Seventy-six patients were included; median age 58 years (interquartile range [IQR] 16), 57% males, median ICU admission APACHE II 27 (IQR 11.3). PICS related impairments were present in 91%, with physical PICS being most common (72%). Duration of phenylephrine infusion ($r_p = .28$, 95% CI: .05, .48) was positively correlated with psychological PICS. Patients exposed to corticosteroids were positively correlated with physical PICS ($r_p = .27$, 95% CI: .04, .47). Exposure to dexmedetomidine ($r_p = -.21$, 95% CI: -.44, -.01) and inhaled epoprostenol ($r_p = -.25$, 95% CI:-.45, -.02) had inverse correlations with psychological and cognitive PICS, respectively.

Conclusions

Symptoms of PICS are commonly found in medical ICU survivors after discharge. Medication use in the ICU may be both positively and negatively correlated with PICS. These data are exploratory and warrant further investigation.

1. INTRODUCTION

Post-intensive care syndrome (PICS) is a public health burden arising from the neuropsychological and functional disability intensive care unit (ICU) survivors experience after a prolonged ICU stay. It is defined as a new or worsening impairment in mental health, cognitive, or physical status that develops after critical illness and persists beyond discharge from the hospital.[1] Its exact prevalence is unknown, with large ranges reported in previous literature.[2] The upper ends of these ranges have been reported around 80% with symptoms occurring not only in the patient but also in their caregivers.[2] Symptoms are also known to persist with at least one symptom present in 64% and 56% of patients at 3 and 12 months after discharge, respectively.[3] The COVID-19 pandemic has further added to this burden as patients with severe illness due to COVID-19 often require prolonged mechanical ventilation due to acute respiratory distress syndrome (ARDS).[2] With the increasing number of ICU survivors during the COVID-19 pandemic, the number of patients at risk for PICS has risen. Data suggests three-quarters of COVID-19 survivors have at least one symptom of PICS 3 months after discharge.[4,5]

To decrease the burden of PICS, modifiable risk factors need to be identified and strategies to mitigate them developed. Reported risk factors include immobility, delirium, agitation, mechanical ventilation, physical restraints, ARDS, sepsis, and multi-organ failure.[1,3,6] Many patients with these conditions receive prolonged sedation, neuromuscular blockade, and systemic glucocorticoids which could potentially provide modifiable medication risk factors of PICS.[7] Therefore, the effect of ICU medication practices on the long term psychological, cognitive, and physical outcomes of PICS represents a gap in the literature and potential modifiable risk factors that warrant investigation.

Identifying medications at highest risk for causing PICS and optimizing their use in the ICU could improve quality of life for ICU survivors after discharge. Therefore, this study aimed to identify specific medication exposures during ICU care that were associated with the development of psychological, cognitive, and physical dysfunctions of PICS.

2. MATERIALS AND METHODS

2.1. STUDY SETTING

This study was performed at an 886-bed academic medical center with 115 adult ICU beds. In April 2020, due to the increasing number of COVID-19 survivors, the institution's Adult Critical Care Services partnered with its home care program to implement the Critical Illness Recovery Program (CIRP). This program provides early home-based interventions to ICU survivors. Until 5/8/2022, all patients admitted to any ICU with a diagnosis of COVID-19 were screened by ICU clinical pharmacists for CIRP eligibility (Supplemental Table 1). Since 5/9/2022 all medical ICU patients, including those without COVID-19, were screened for CIRP eligibility. The program is offered to all eligible patients discharged to a location within the home care program's region of coverage. Enrollment in CIRP includes home healthcare services beginning immediately after hospital discharge and two virtual interdisciplinary telehealth visits (including provider, nurse, clinical pharmacist, and social worker), the first within 2-3 weeks and the second within 3 months after hospital discharge. The goal is to identify PICS symptoms, reduce symptom burden, improve physiological, cognitive, and functional recovery, optimize medication therapy, and offer targeted outpatient care. Various standardized assessments are used to identify the manifestations of PICS and their progression over time. These assessments take place within the first 2 weeks after discharge and at 3 months and include the Patient Health Questionnaire (PHQ-9) for depression, the Generalized Anxiety Disorder score (GAD-7) for anxiety, the Primary Care-PTSD-Screen for DSM-5 (PC-PTSD-5) for post-traumatic stress disorder (PTSD), the Saint Louis University Mental Status examination (SLUMS) for cognitive impairment, and the Short Physical Performance Battery (SPPB) for physical functioning.[8-12] Qualified and experienced social workers on the team were responsible for administering these standardized assessments.

2.2. STUDY DESIGN

This was a retrospective study exploring the potential association of medications used in the ICU with the development of PICS. Adult patients aged 18-89 years admitted to an ICU between April 1, 2020, and July 31, 2023, who were enrolled in CIRP and had a CIRP clinic note documented after discharge were included. Those without documentation for screening for symptoms of PICS were excluded. This study met federal and university criteria for exemption by the organization's Research Subjects Review Board and patient consent was waived. The guidelines for reporting observational studies of Strengthening the Reporting of Observational Studies in Epidemiology checklist was used to strengthen the reporting of our findings.

2.3. STUDY OUTCOMES AND DATA COLLECTION

The outcomes of interest were psychological, cognitive, and physical PICS symptoms. New or worsened PICS symptoms from baseline were identified from the electronic health record (EHR) screening forms or documentation from the physician's clinic note if screening forms unavailable. A PHQ-9 score $\geq$ 5 (includes mild to severe depression), GAD-7 score $\geq$ 5 (includes mild to severe anxiety), PC-PTSD-5 score $\geq$ 3 (associated with higher likelihood of PTSD), SLUMS score $\leq$ 26 (at least mild neurocognitive disorder), or SPPB score < 7 (associated with rehospitalization and mortality) were considered positive for presence of PICS.[8-12]

Medication exposures collected via EHR review included continuous infusions of sedatives, vasopressors, inotropes, and neuromuscular blocking agents, as well as corticosteroids, antibiotics, intermittent benzodiazepines and opioids, inhaled epoprostenol, blood products, antidepressants, antipsychotics, and antihistamines. Maximum dose and duration of exposure to select medications were also

Table 1. Medication Exposure Definitions

Medications	Exposure Definition	Variables Analyzed
Continuous Sedation • Fentanyl[a] • Hydromorphone[a] • Dexmedetomidine • Propofol • Midazolam • Ketamine	At least 4 hours of continuous infusion at any dose	Exposure (Yes/No) Maximum Rate Duration
Continuous Vasopressors • Norepinephrine[b] • Epinephrine[b] • Phenylephrine[b] • Dopamine[b] • Vasopressin	At least 4 hours of continuous infusion at any dose	Exposure (Yes/No) Maximum Rate Duration
Continuous Inotropes • Dobutamine • Milrinone	At least 4 hours of continuous infusion at any dose	Exposure (Yes/No) Maximum Rate Duration
Continuous Neuromuscular Bocking Agents • Cisatracurium • Atracurium	At least 4 hours of continuous infusion at any dose	Exposure (Yes/No) Duration
Corticosteroids	At least 20 mg prednisone equivalence for at least 48 hours	Exposure (Yes/No) Maximum Daily Dose Duration
Antibiotics	Any dose of an antibiotic agent for at least 48 hours	Exposure (Yes/No) Duration
Intermittent Benzodiazepines	At least 2 doses of any benzodiazepine AND not on continuous benzodiazepine infusion (IV or PO)	Exposure (Yes/No) Duration
Intermittent Opioids	At least 2 doses of any opioid AND not on continuous opioid infusion (IV or PO)	Exposure (Yes/No) Duration
Inhaled Epoprostenol	Exposure at any dose and duration	Exposure (Yes/No) Duration
Blood Products • Packed Red Blood Cells • Fresh Frozen Plasma • Platelets • Cryoprecipitate	Exposure at any dose and duration	Exposure (Yes/No)
Miscellaneous Medications • Antidepressant • Antipsychotic • Antihistamine	Any dose of an agent for at least 48 hours	Exposure (Yes/No) Duration

[a]Maximum dose recorded in morphine equivalents for continuous opioids (200 mcg/hr fentanyl = 10 mg/hr morphine = 1.5 mg/hr hydromorphone)
[b]Maximum dose recorded in norepinephrine equivalents for catecholamines (norepinephrine 0.1 mcg/kg/min = 0.1 mcg/kg/min epinephrine = 200 mcg/min phenylephrine = 10 mcg/kg/min dopamine)

collected. Definitions of exposures and dose equivalents used for comparison of maximum dose are in Table 1.

Additional data collected included patient demographics and descriptors such as age, race, weight, sex, body mass index (BMI), COVID-19 positivity, admitting diagnosis, hospital and ICU length of stay (LOS), APACHE II score on ICU admission, Charlson Comorbidity Index (CCI), highest Sequential Organ Failure Assessment (SOFA) score during the first 7 days of ICU admission, rate of delirium (days with a positive Confusion Assessment Method for the ICU compared to total ICU LOS), and duration of deep sedation (total days with any Riker Sedation Agitation Scale score ⩽ 2). Investigators extracted data from the EHR using a standardized case report form developed in REDCap (Research Electronic Data Capture) and data dictionary to reduce variability.

2.4. STATISTICAL ANALYSIS

The small case-to-variable ratio precluded inferential methods for identifying possible best correlates, so an effect size-based, method was used consisting of two steps. In the first step, bivariate correlations between covariates and each of the three PICS outcome variables, psychological, cognitive, and physical, were generated (point-biserial and phi coefficients for numeric and categorical correlates,

respectively). Bivariate relationships with r ⩾ .20 were defined as clinically relevant correlates of the outcome (based on convention that r's between .2 and .5 are moderately-sized) and subject to further analysis.

To control for relationships among bivariate correlates of a PICS outcome, a second step in the analysis generated partial correlation coefficients for the set of variables of each outcome. Relationships with partial correlations (r_p) ⩾ .20 were regarded as clinically significant. This analysis therefore identified the possible best correlates of each PICS outcome variable by controlling for the variables' interdependence including the medication variables as well as demographic and background variables of age ⩾ 65 years, rate of delirium, deep sedation, and APACHE II scores. Significance testing was not used in the analysis because the small sample and large number of relationships would create a corrected alpha level (to control the type I error rate) so small as to effectively preclude any relationship being significant.

3. RESULTS

3.1. STUDY POPULATION

A total of 77 patients had a CIRP visit during the study time frame. After excluding one patient who was not screened for PICS, 76 patients were included in the study. The baseline characteristics are reported in Table 2. The population was severely ill, and about two thirds had a positive COVID-19 test.

3.2. STUDY OUTCOMES

The overall incidence of patients who had at least one symptom of PICS was 91% with the most common PICS symptom being physical (72%), followed by cognitive (64%), and psychological (38%). Bivariate correlations (phi coefficients) among the PICS outcome variables were small and nonsignificant, indicating that the presence of one PICS symptom was not associated with the presence of any other (Table 3).

The incidence of PICS diagnoses by medication exposure is listed in Supplemental Table 2. Duration of phenylephrine, controlling for other covariates, was positively associated with the presence of psychological PICS (r_p = .28, 95% CI: .05, .48). On the other hand, exposure to dexmedetomidine was negatively associated with psychological PICS (r_p = -.21, 95% CI: -.44, -.01). Exposure to inhaled epoprostenol (r_p = -.25, 95% CI:-.45, -.02) was the only clinically relevant association with cognitive PICS. Exposure to corticosteroids (r_p = .27, 95% CI: .04, .47) was the only clinically relevant relationship associated with physical PICS. These relationships were present while controlling for the non-medication covariate risk factors of age, rate of delirium, days spent in deep sedation, and severity of illness (APACHE II score).

Bivariate (and partial, r_p) correlations of covariates with each PICS outcome variable that were determined to be clinically relevant associations (r ⩾ .20) are in Table 4. Partial correlations controlled for the other covariates in the group. Due to their independence, outcome variables were not partialled. As part of the preliminary analysis, all variable correlations analyzed are in Supplemental Table 3.

4. DISCUSSION

To our knowledge, this is the first study to investigate associations between ICU medication use only and all PICS symptoms. We found medications with both positive and negative correlations with individual PICS symptoms. These findings provide insight that can be translated into clinical changes and modifiable factors, although these relationships should be explored further. This study also adds to the growing body of literature reporting the common occurrence of PICS in critical care populations.

The exact prevalence of PICS in ICU survivors is unknown due to poor recognition, a lack of follow-up care, variability in patient screening, and differences in patient populations studied. A recent study of over 2,000 ICU survivors analyzed baseline status as well as PICS symptoms one year after ICU admission.[13] PICS was present in 58%, 64%, and 43% medical, urgent surgical, and elective surgical patients, respectively.[13] Our study found a higher incidence of PICS symptoms overall compared to this previous report. This may be due to our inclusion of a strictly medical ICU population with many having COVID and a long ICU LOS, possibly representing a much more critically ill population. We also screened patients weeks and months after discharge compared to a year later which may have caused these differences. An analysis looking at subtypes of PICS symptoms, the ARDS Network Long-Term Outcomes Study (ALTOS), identified four distinct subtypes based on baseline predictors and health status at six months.[14] This study found that a large majority of evaluated patients had at least one PICS symptom, which was also true in our study. The ALTOS study also found physical and mental status after discharge to be closely associated, but cognitive status was not.[14] Uniquely in our study, when assessing the correlation between psychological, cognitive, and physical PICS symptoms, the association was small and insignificant, showing PICS symptoms were independent of each other. This strengthens our analysis by allowing the interpretation of the associations without correlation of the outcomes' variables.

Previous literature seeking to identify PICS risk factors have focused mostly on non-medication risk factors or medication risk factors for a single PICS symptom. When looking at cognitive impairment, one study specifically reported frequent, severe delirium and advanced age predispose patients to developing cognitive PICS.[15] Similarly, another study reported the most significant independent risk factor for cognitive PICS is ICU delirium.[16] There are many risk factors for delirium in ICU patients including use of certain classes of medications.[17] We analyzed a variety of these potentially deliriogenic medications including benzodiazepines, antihistamines, and steroids, however none were highly correlated with cognitive symptoms after controlling for group covariates. Exposure to inhaled

Table 2. Baseline Characteristics

Baseline Characteristic	Patient Population (n=76)
Age, median (IQR) years	58 (16.5)
Sex, n (%) Female Male	 33 (43.4) 43 (56.6)
Race, n (%) Black or African American Caucasian Asian American Indian or Alaskan Native Native Hawaiian or Pacific Islander Other	 21 (27.6) 47 (61.8) 3 (3.9) 1 (1.3) 0 4 (5.3)
BMI, median (IQR)	31.9 (10.7)
COVID positivity, n (%)	51 (67.1)
Admitting diagnosis, n (%)[a] Respiratory Infectious Cardiovascular Neurologic Gastrointestinal Metabolic Other	 60 (78.9) 57 (75) 10 (13.2) 6 (7.9) 4 (5.3) 2 (2.6) 2 (2.6)
Apache II Score, median (IQR)	27 (11.3)
Charleston Comorbidity Index, median (IQR)	2.5 (3)
SOFA Score, (%) 6-7 8-9 10-11 12-14 >14	 2 (2.6) 10 (13.2) 10 (13.2) 35 (46.1) 19 (25)
ICU LOS, median (IQR) days	17 (22)
Hospital LOS, median (IQR) days	28.5 (24.5)

[a]Patients could have had multiple admitting diagnoses.
Abbreviations: IQR = interquartile range, BMI = body mass index, SOFA = sequential organ failure assessment, ICU = intensive care unit, LOS = length of stay

Table 3. Correlations (95% CI) of PICS outcome variables

Variable	Psychological	Cognitive
Psychological	----	----
Cognitive	.13 (-.10, .35)	----
Physical	.06 (-.17, .28)	.09 (-.13, .31)

Note. Correlations are phi coefficients among the PICS outcome variables.
Abbreviations: CI = confidence interval

epoprostenol was the only analyzed medication risk factor shown to be negatively correlated with cognitive PICS. This could be an incidental finding without a known mechanistic explanation. However, epoprostenol has been shown to improve oxygenation in mechanically ventilated patients with severe hypoxia.[18] Whether these effects on oxygenation could affect long-term cognitive impairment is currently unknown and should be explored further.

There is one study that assessed risk factors for psychological morbidity three months after intensive care and found the strongest clinical risk factor for PTSD was longer duration of sedation, and there was a strong association between depression and benzodiazepine administration.[19] They also found use of inotropes and vasopressors to be correlated with presence of anxiety.[19] In our study, psychological PICS included anxiety, depression, or PTSD and was found to be positively correlated with increasing durations of phenylephrine infusions. Patients receiving phenylephrine for longer durations may also be confounded by the severity of illness since 83% of patients on phenylephrine continuous infusion required more than one vasopressor and these patients also had longer ICU and hospital LOS. Vasopressor choice was at the provider's discretion at the time of ordering and along with these other potential confounders, it is difficult to differentiate this association further with the limited sample size and retrospective study

Table 4. Bivariate (and partial, r_p) correlations of covariates with PICS outcome variables

Covariate	Psychological	Cognitive	Physical
Vasopressin Infusion Maximum Rate	-.32 (-.06)	----	----
Vasopressin Infusion Duration	-.28 (-.12)	----	----
Dexmedetomidine Infusion Exposure	-.21 (-.24[a])	----	----
Phenylephrine Infusion Duration	.32 (.28[1])	----	----
Inhaled Epoprostenol Exposure	----	-.25 (-.26[a])	----
Intermittent Opioid Exposure	----	-.22 (-.02)	----
Intermittent Benzodiazepine Exposure	----	.21 (-.02)	----
Fentanyl Infusion Exposure	----	.27 (.19)	----
Any Vasopressor/inotrope Infusion Duration	----	----	.24 (-.13)
Norepinephrine Infusion Duration	----	----	.26 (.16)
Corticosteroid Exposure	----	----	.28 (.27[a])

Note. Data are displayed as bivariate correlations followed by r_p in parentheses. Correlations are phi coefficients for exposure variables and point-biserial coefficients for dose and duration variables. Within each PICS outcome, partial correlations show the relationship of each correlate of the outcome controlling for the other variables.
[a]A clinical-relevance threshold of $r_p \geq \pm 0.20$ was used for reporting and interpretation. Variables that are clinically relevant using these criteria are in Table 4. See Supplemental Table 3 for analysis of all variables.

design. Exposure to dexmedetomidine in our study was correlated with a decrease in the presence of psychological PICS. Previous literature assessing dexmedetomidine use in the ICU has shown benefit with shorter time to extubation and less coma/delirium compared to other continuous sedatives.[20,21] We hypothesize our finding could be due to its properties as an anxiolytic medication as well as the beneficial effects of earlier extubation and shorter duration of delirium.

Physical manifestations of PICS can range from short term oxygen requirements to significant limitations including inability to perform activities of daily living or return to work. In our study, corticosteroid exposure was the only clinically relevant medication found to be associated with physical impairment. This relationship has been previously reported in a systematic review and meta-analysis of 17 prospective studies with over 2,000 patients that evaluated the effect of corticosteroids on ICU-acquired weakness.[22] Corticosteroid administration was significantly associated with an increased odds of developing ICU-acquired weakness with an incidence of 43% in the corticosteroid group compared to 34% in the control group.[22] Cumulative doses of corticosteroids were also found to be significantly higher in patients who developed ICU-acquired weakness, but duration of corticosteroids was not an independent risk factor.[22] In our study, both duration and increasing cumulative doses of corticosteroids were not correlated with physical PICS outcome, only exposure. This suggests corticosteroid exposure (defined as administration of ⩾ 20 mg prednisone equivalent at any time) may be more important than the maximal dose or duration in the development of physical impairments. This finding provides additional rationale for avoiding such corticosteroid use unless there are clear clinical indications.

Our study has many strengths. To our knowledge, this is the first study assessing medication risk factors only and their correlations with all PICS components. We were also able to control for potential covariate non-medication risk factors including advanced age, delirium, deep sedation, and severity of illness (APACHE II score). Also, despite the retrospective design, the method of follow up and PICS symptom analysis after discharge from the ICU was the same for each enrolled patient due to the protocolization of our CIRP. Finally, since these data are exploratory and hypothesis generating, several future research questions could be developed expanding on this investigation in a growing critical patient population.

Our study has several limitations. First, we did not have baseline PICS symptom questionnaires available for patients, potentially over-estimating the prevalence of PICS if patients had baseline symptoms not captured via EHR review. Second, since this is the first study of its kind, the definitions of medication exposure were developed based on individual medication onset and duration of action or their clinical relevance as determined by available literature and investigator team judgement rather than robust previously reported protocols. Third, these findings were only analyzed in a critically ill patient population followed up in the CIRP, which may have limited the sample size, but provided homogeneity in the population. Further, there was no control group for comparison. Patients who met criteria for CIRP but were not seen due to death, discharge out of the area, or patient decline may have introduced selection bias into our study population. Also, about two thirds of our study population had COVID-19 which makes findings difficult to apply to general practice. Finally, we did not do significance testing as described in the methods, therefore results can only be exploratory and hypothesis generating. However, not testing for significance eliminated the chance of an inflated type I error that could have occurred with a small sample size and large number of tested relationships. Using bivariate and partial correlation of covariates instead allowed us to still assess relationships of the analyzed variables based on effect size while controlling for predictors of PICS.

5. CONCLUSIONS

The incidence of PICS is increasing as more patients survive to discharge after intensive care. The present study found over 90% of the enrolled patients had at least one symptom of PICS. These exploratory data suggest phenylephrine duration and exposure to corticosteroids may be correlated with a higher risk of PICS symptoms. In contrast, dexmedetomidine and inhaled epoprostenol suggest a protective negative correlation with PICS symptoms. These relationships were discovered using exploratory analyses and are hypothesis generating. Further definitive studies are needed.

ABBREVIATIONS

ARDS, advanced respiratory distress syndrome; BMI, body mass index; CCI, Charlson Comorbidity Index; CI, confidence interval; CIRP, Critical Illness Recovery Program; GAD-7, Generalized Anxiety Disorder score; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; PC-PTSD-5, Primary Care-PTSD-Screen for DSM-5; PHQ-9, Patient Health Questionnaire; PICS, post-intensive care syndrome; PTSD = post-traumatic stress disorder; REDCap, Research Electronic Data Capture; SLUMS, Saint Louis University Mental Status examination; SOFA, sequential organ failure assessment; SPPB, Short Physical Performance Battery

SUPPLEMENTAL MATERIAL

The Supplemental Data file for Supplemental Tables 1, 2 and 3 is available and uploaded.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are not publicly available due to privacy/ethical reasons as we do not have permission to share from our research review board nor have consent from enrolled subjects. Data may be available through a data use agreement upon reasonable request.

AUTHOR CONTRIBUTIONS

KH, AS, AP, CG designed the research study. KH, AS, AP, BB, AB, AR, WS, CG performed the research. KH, AS, and BB analyzed the data. KH, AS, AP, BB, AB, AR, WS, CG interpreted the data. KH, AS, CG wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted in accordance with the Declaration of Helsinki. The research protocol was approved by the University of Rochester Medical Center Research Subjects Review Board (Approval number: STUDY00008781) with a waiver of consent.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DECLARATION OF AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work the authors have not used AI or AI-assisted technologies.

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