

Associations of Race With Sedation Depth Among Mechanically Ventilated Adults: A Retrospective Cohort Study

OBJECTIVES: To evaluate the association of race with proportion of time in deep sedation among mechanically ventilated adults.

DESIGN: Retrospective cohort study from October 2017 to December 2019.

SETTING: Five hospitals within a single health system.

PATIENTS: Adult patients who identified race as Black or White who were mechanically ventilated for greater than or equal to 24 hours in one of 12 medical, surgical, cardiovascular, cardiothoracic, or mixed ICUs.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: The exposure was White compared with Black race. The primary outcome was the proportion of time in deep sedation during the first 48 hours of mechanical ventilation, defined as Richmond Agitation-Sedation Scale values of -3 to -5 . For the primary analysis, we performed mixed-effects linear regression models including ICU as a random effect, and adjusting for age, sex, English as preferred language, body mass index, Elixhauser comorbidity index, Laboratory-based Acute Physiology Score, Version 2, ICU admission source, admission for a major surgical procedure, and the presence of septic shock. Of the 3337 included patients, 1242 (37%) identified as Black, 1367 (41%) were female, and 1002 (30%) were admitted to a medical ICU. Black patients spent 48% of the first 48 hours of mechanical ventilation in deep sedation, compared with 43% among White patients in unadjusted analysis. After risk adjustment, Black race was significantly associated with more time in early deep sedation (mean difference, 5%; 95% CI, 2–7%; $p < 0.01$).

CONCLUSIONS: There are disparities in sedation during the first 48 hours of mechanical ventilation between Black and White patients across a diverse set of ICUs. Future work is needed to determine the clinical significance of these findings, given the known poorer outcomes for patients who experience early deep sedation.

KEYWORDS: critical care outcomes; deep sedation; healthcare disparities; intensive care units; respiratory failure

Sedation during mechanical ventilation reduces the physiologic stress of organ dysfunction and assuages pain, anxiety, and distress to promote patient safety (1). However, early deep sedation, defined by a Richmond Agitation-Sedation Scale (RASS) value of -3 to -5 in the first 48 hours of mechanical ventilation, is associated with delayed extubation (2, 3), longer ICU and hospital lengths of stay (3–5), and increased mortality (2–4, 6, 7). Limiting the intensity and duration of sedation is therefore important to optimize these clinical outcomes, as well as other patient-centered outcomes, such as mobility and short- and long-term cognitive function (8, 9). Black patients with acute respiratory failure experience worse clinical outcomes compared with

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KEY POINTS

Question: Is the depth of sedation during the first 48 hours of mechanical ventilation different for Black and White adults in the ICU?

Findings: In a retrospective cohort study of mechanically ventilated adults across 12 ICUs within a single, large health system, Black race was significantly associated with more time in early deep sedation, defined as a Richmond Agitation-Sedation Scale of -3 to -5 in the first 48 hours of mechanical ventilation (mean difference, 5%; 95% CI, 2–7%; $p < 0.01$), compared with White race.

Meaning: Disparities in the depth of sedation during the first 48 hours by race not only exist, but merit further investigation, given the implications of early deep sedation on clinical outcomes.

White patients (10); however, the mechanisms underlying this difference have not been elucidated (11, 12). Sedation practices in ICUs are heterogeneous and variability in patient responses to sedatives and analgesics may be implicated in worse outcomes. Racial disparities are present in the treatment of pain (13, 14), but have never been evaluated in sedation practices. Therefore, our objective was to evaluate associations of race with the depth of sedation among mechanically ventilated adults. We hypothesized that Black patients experience longer early deep sedation compared with White patients.

MATERIALS AND METHODS

We performed a retrospective cohort study of adults older than 18 years requiring mechanical ventilation for greater than or equal to 24 hours across five urban and suburban hospitals within a large health system from October 2017 to December 2019. Of the 12 ICUs included in the cohort, eight are specialty ICUs located within two urban academic tertiary care hospitals with greater than 500 hospital beds that serve as regional referral centers; two are specialty ICUs located within a smaller urban hospital with a limited number of residency programs; and two are ICUs with mixed patient populations within smaller community-based hospitals in suburban locations. Patients were

included only if their documented race was Black or White in the electronic health record. Non-White and non-Black patients represented 10% (573/5667) of the entire population, and subgroups within that group were exceedingly small, and so they were excluded. Additionally, disparities in outcomes for patients with acute respiratory failure are specifically noted between Black and White patients (10). Additional exclusion criteria included admission to neurologic/neurosurgical ICUs, tracheostomy before admission, and dementia before admission, as sedation practices may be tailored in these populations, rather than capturing routine practice (1, 2). We also excluded patients with greater than or equal to 8 hours between the start of mechanical ventilation and the first recorded RASS, given this was a significant proportion of time during the first 48 hours at an unknown RASS (i.e., the patient was at a procedure or a clinical emergency precluded documentation).

The exposure was White vs. Black race. The primary outcome was early deep sedation, defined as the proportion of time during the first 48 hours of mechanical ventilation that patients were alive, in the ICU, and with a RASS -3 to -5 . Secondary outcomes included: 1) average sedation intensity within the first 48 hours, defined as the average RASS value, weighted by duration of time at that value and 2) deep sedation for the entirety of the first 48 hours of mechanical ventilation (binary). RASS documentation frequency was variable across study ICUs. Therefore, in order to estimate the duration of time that a patient spent at a given RASS, we created an hour-level dataset and carried forward a RASS value for each hour until a new RASS was documented.

We included descriptive statistics for Black and White patients, using the Wilcoxon rank-sum test (two groups) or Kruskal-Wallis test (more than two groups) for continuous variables and Pearson chi-square test for categorical variables. We then performed unadjusted and adjusted analyses using mixed-effects linear and logistic regression models at the patient level including ICU as a random effect to account for nonindependence of observations within ICUs. Covariates in adjusted models included age, sex, English as preferred language, body mass index (BMI), Elixhauser comorbidity index, Laboratory-based Acute Physiology Score, Version 2 (LAPS2), ICU admission source, admission for a major surgical procedure, and presence

of septic shock. Covariates were chosen a priori based on literature review related to early deep sedation (2, 3) as well as how depth of sedation may implicate different outcomes in select groups (i.e., older patients [15]). LAPS2 was chosen instead of the Sequential Organ Failure Assessment score given less racial bias for in-hospital mortality prediction (16). We used linear splines with five knots for age, Elixhauser comorbidity index, and LAPS2 for the adjusted analyses to allow for the possibility of nonlinear relationships. Three patients were missing BMIs and therefore excluded from adjusted analyses. A p value of less than 0.05 was used for statistical significance in all analyses.

We performed four sensitivity analyses for the primary outcome: 1) we assessed deep sedation during the first 72 hours of mechanical ventilation to address a common time point of enrollment for patients with acute respiratory failure in clinical trials, 2) we only included patients with a documented RASS within 2 hours of mechanical ventilation initiation to understand whether patients with missing data in the first 8 hours of mechanical ventilation represented a different population, 3) we excluded patients who had been extubated within the first 48 hours of ICU admission, and 4) we excluded patients who required continuous paralytics at any point during their ICU stay.

This study, under the title of “Retrospective cohort of ICU patients” and protocol number 830161 was reviewed and approved by the University of Pennsylvania Institutional Review Board on February 1, 2022. Procedures were followed in accordance with the ethical standards of our institution’s responsible committee on human experimentation and with the Helsinki Declaration of 1975.

RESULTS

Across the 12 ICUs in our cohort, 3337 patients met inclusion criteria, of whom 1242 (37%) identified as Black (**Appendix Fig. 1**, <http://links.lww.com/CCX/B263>). The median age was 64 (interquartile range [IQR], 53–73) and 1367 (41%) were female. One thousand five hundred sixty-nine patients (47%) were admitted from the emergency department, and 1735 (52%) were admitted for a major surgical procedure. Time on mechanical ventilation, and ICU length of stay were similar between Black and White patients, whereas tracheostomy placement, in-hospital mortality, and

hospital length of stay were significantly different in unadjusted analyses. Black patients were younger (median age, 61 [IQR, 50–71] vs. 65 [IQR, 55–74]), more often female (47% vs. 37%), less frequently English as preferred language (2% vs. 4%), had higher Elixhauser comorbidity indices 15 (IQR 8–22) vs. 14 (IQR 7–21), and less often admitted for a major surgical procedure (43% vs. 57%).

There was a median of 16 RASS values recorded in the first 48 hours of mechanical ventilation, with no significant differences between Black and White patients ($p = 0.33$). The median time to documentation of first RASS after the initiation of mechanical ventilation was 1 hour for both Black and White patients (**Table 1**; and **Appendix Fig. 2**, <http://links.lww.com/CCX/B263>). The median time between RASS measurements was 3.2 hours for White patients and 3.1 hours for Black patients (Table 1; and **Appendix Fig. 3**, <http://links.lww.com/CCX/B263>).

In unadjusted models, Black patients spent 44% of time in deep sedation during the first 48 hours of mechanical ventilation, compared with 41% among White patients, although this did not meet statistical significance (mean difference, 3%; 95% CI, 0.1–5%; $p = 0.06$). In adjusted models, Black patients spent 48% of the first 48 hours of mechanical in ventilation compared with 43% for White patients (mean difference, 5%; 95% CI, 2–7%; $p < 0.01$) (**Table 2**). The proportion of time in the first 48 hours spent in deep sedation had a bimodal distribution (**Appendix Fig. 4**, <http://links.lww.com/CCX/B263>).

Black patients had a significantly higher sedation intensity (i.e., lower average RASS) compared with White patients during the first 48 hours of mechanical ventilation (unadjusted difference in average RASS: 0.11 [95% CI, 0.01–0.21; $p = 0.03$] and adjusted: 0.18 [95% CI, 0.08–0.28; $p < 0.01$]). The sedation intensity or average RASS for Black vs. White patients in the first 48 hours was -2.2 vs. -2.1 in unadjusted models (95% CI, -2.5 to -2.0 vs. -2.3 to -1.9 ; $p < 0.01$) and -2.4 vs. -2.2 in adjusted models (95% CI, -2.4 to -2.3 vs. -2.2 to -2.1 ; $p < 0.01$).

In unadjusted models, Black patients had 1.4 higher odds of spending the entirety of their first 48 hours of mechanical ventilation in deep sedation compared with White patients (95% CI, 1.1–1.8; $p < 0.01$). This was unchanged in adjusted models (predicted probability of spending first 48 hr in deep sedation for Black

TABLE 1.
Cohort Characteristics and Unadjusted Clinical Outcomes^a

Characteristic	Black (n = 1242)	White (n = 2095)	p
Age, median (IQR)	61 (50–71)	65 (55–74)	< 0.01
Female sex	586 (47)	781 (37)	< 0.01
Body mass index, median (IQR)	28.1 (23.2–34.7)	27.8 (23.6–32.9)	0.10
Hispanic ethnicity	42 (3)	65 (3)	0.66
English as preferred language	1214 (98)	2022 (97)	0.05
Insurance type			< 0.01
Private	217 (17)	610 (29)	
Medicare	604 (49)	1120 (53)	
Medicaid	361 (29)	184 (9)	
Other ^b	60 (5)	181 (9)	
Elixhauser comorbidity index, median (IQR)	15 (8–22)	14 (7–21)	< 0.01
Laboratory-based Acute Physiology Score, Version 2 score (worst in ICU), median (IQR)	157 (125–190)	155 (123–187)	< 0.01
Admission source			< 0.01
Emergency department	821 (66)	748 (36)	
Outside hospital	303 (24)	886 (42)	
Direct admission	118 (10)	461 (22)	
ICU type (number of ICUs)			< 0.01
Medical (3)	498 (40)	504 (24)	
Cardiothoracic (2)	272 (22)	605 (29)	
Surgical (2)	264 (21)	391 (19)	
Cardiac (2)	108 (9)	189 (9)	
Mixed (3)	100 (8)	406 (19)	
Admission for a major surgical procedure	533 (43)	1202 (57)	< 0.01
Presence of septic shock during hospitalization	420 (34)	784 (37)	0.04
Use of restraints during ICU stay	1042 (84)	1773 (85)	0.57
Continuous paralytic infusion exposure ^c	225 (18)	342 (16)	0.18
Continuous benzodiazepine infusion exposure ^c	271 (22)	499 (24)	0.19
Unadjusted clinical outcomes			
In-hospital mortality	341 (28)	636 (30)	< 0.01
Time on mechanical ventilation (d), median (IQR)	3.4 (1.8–7.4)	3.5 (1.8–7.5)	0.88
ICU LOS (d), median (IQR)	6.6 (3.6–12.7)	6.9 (3.8–13.2)	0.13
Hospital LOS (d), median (IQR)	14.5 (7.6–26.2)	16.2 (9.1–29.0)	< 0.01
Readmission to ICU during hospitalization	186 (15)	398 (19)	< 0.01
Tracheostomy placed during hospitalization	192 (16)	371 (18)	< 0.01
Other			
Time to first RASS after the start of mechanical ventilation, median (IQR)	1 (0–2)	1 (0–2)	0.13
Time between RASS measurements, median (IQR)	3.2 (2.5–3.7)	3.1 (2.4–3.7)	0.06

IQR = interquartile range, LOS = length of stay, RASS = Richmond Agitation-Sedation Scale.

^an (%) unless otherwise indicated.

^bOther insurance includes workman's compensation, self-pay, charity, enrolled in a study, hospice, veteran's association, or missing.

^cExposures are at any point during the patient's ICU stay, not necessarily during the first 48 hr of mechanical ventilation.

TABLE 2.
Adjusted Associations of Race With Sedation^a

Primary Outcome	Beta Coefficient (95% CI) in Percent Time of 48 hr	<i>p</i>	Adjusted Predicted Time in Deep Sedation (95% CI)
Time in early deep sedation			
White (reference)	0.05 (0.02–0.07)	< 0.01	White: 43% (42–45%)
Black			Black: 48% (46–50%)
Secondary Outcomes			
Average sedation intensity	Beta Coefficient (95% CI)		Adjusted Predicted Average Richmond Agitation-Sedation Scale (95% CI)
White (reference)	0.18 (0.08–0.28)	< 0.01	White: –2.2 (–2.2 to –2.1)
Black			Black: –2.4 (–2.4 to –2.3)
First 48 hr in deep sedation	Odds Ratio (95% CI)		Adjusted Predicted Probability (95% CI)
White (reference)	1.4 (1.1–1.8)	< 0.01	White: 0.12 (0.09–0.15)
Black			Black: 0.16 (0.12–0.19)

^aAdjusted for age, gender, body mass index, Elixhauser comorbidity index, Laboratory-based Acute Physiology Score, Version 2, English as preferred language, hospital admission source, admission for a major surgical procedure, and presence of septic shock.

vs. White patients [0.16 (95% CI, 0.12–0.19) vs. 0.12 (95% CI, 0.09–0.15)]; $p < 0.01$).

Results were similar across sensitivity analyses (Appendix Table 1, <http://links.lww.com/CCX/B263>).

DISCUSSION

In this retrospective cohort study of mechanically ventilated patients admitted to 12 ICUs of five hospitals, Black patients spent a longer proportion of the first 48 hours of mechanical ventilation in deep sedation at a RASS of –3 to –5, had a more negative average RASS during the first 48 hours of mechanical ventilation, and were more likely to remain deeply sedated throughout the first 48 hours of mechanical ventilation compared with White patients. To our knowledge, this is the first study to evaluate disparities in depth of sedation among adult mechanically ventilated patients. Given the relationship between early sedation management and clinical outcomes (2–4), these differences may contribute to racial disparities in outcomes after critical illness and mechanical ventilation.

Black patients spent additional time in deep sedation and had small differences in the average RASS during the first 48 hours of mechanical ventilation. The large sample size and diversity of ICUs

signals that depth of sedation may indeed differ by race, which differs somewhat from a previous study in critically ill pediatric patients where there was a lack of distinct patterns in sedation management that consistently favored one race or ethnicity over another (17). Our current processes for systematic assessment of sedation depth and intensity may not be equitable, as landmark trials in sedation practices enroll limited numbers of non-White patients (1, 18, 19), pain management practices continue to differ by race in acute care settings (14), and we have not directly measured how implicit bias mediates sedation practices (17). Although the distribution is bimodal for the primary outcome, a binary outcome of spending the entirety of the first 48 hours in deep sedation is also statistically significant, favoring less deep sedation in White patients.

Furthermore, the clinical implications of these differences are unknown. We note that in this cohort, despite findings of deeper earlier sedation, Black patients actually had shorter average length of stay and lower likelihood to have tracheostomies, for example, which is in contrast with prior evidence associating deeper sedation with longer length of stay and duration of mechanical ventilation. However, these were unadjusted estimates of clinical outcomes that do not represent the risk-adjusted estimates by race. Further analyses

to evaluate the independent relationship of sedation depth with these outcomes were outside of the scope of this study, and prospective research is needed to further understand the clinical significance of our results. It is possible that small differences in deep sedation during the first 48 hours of critical illness may be significant in certain patients, particularly those who only require brief periods of mechanical ventilation. For example, lighter sedation may facilitate a spontaneous awakening and breathing trial, and ultimately allow for earlier extubation (20). Differences in sedation depth may also contribute to the cascade of downstream delirium and cognitive dysfunction suffered by individuals who require longer mechanical ventilation or time in the ICU. The shorter lengths of stay and fewer tracheostomies for Black patients may or may not indicate a better patient-centered outcome for these patients and, therefore point to areas in which we need robust exploration of mechanisms. For example, does shorter length of stay on an index admission then implicate subsequent readmission or worse 90-day outcomes because these patients have fewer resources coordinated at discharge? Do fewer tracheostomies implicate biases in our communication about the long-term prognosis and resources needed for recovery with a tracheostomy for ventilator-dependent respiratory failure? Each question has unique considerations and confounders and future studies should include independent prospective exploration.

Our data adds to the argument that Black patients should be recruited into prospective and randomized clinical trials of sedation strategies to better reflect the diverse population to which we apply these principles. Sedation practices and protocols in diverse ICUs should be examined for clinician bias in assessment of level and depth of sedation based on currently validated scoring systems, ideally measured against goal RASS values set by the clinical team. Daily RASS goals were not captured in the electronic health record for this cohort but would it would be of significant value to explore sedation practices in the context of RASS goal-directed care. Prospective comparison of sedation assessment in racial and ethnic minority patients are specifically needed to explore whether bias exists in measurement of sedation depth and delirium.

There are limitations to this study. RASS values were not collected prospectively. We could not account for the possibility that some patients may require deep

sedation and that this may differ by patient race; however, we attempted to address this at least in part, for example, by excluding neuro-ICUs at study hospitals and by accounting for severity of illness. The median number of RASS scores collected per patient was 16 in 48 hours. However, there may have been instances where RASS scores were collected more or less frequently. We also lack specific information on spontaneous awakening and breathing trials for each patient, details about preceding sedation in patients who were transferred from outside hospitals, and whether those admitted for major surgical procedures required repeat surgery in the first 48 hours. This study, however, represents real-life practice better than explanatory trial cohorts, and therefore is likely widely generalizable to common practices in other urban and suburban ICUs. Additionally, we do not know the clinical relevance of using RASS as a proxy for outcomes related to sedation. Furthermore, we do not provide specific information on cumulative dosing of sedative, analgesic, and paralytic agents in our model. Current literature more readily connects cumulative dosage with delirium outcomes (1, 21), and one prior prospective study demonstrated mixed results with regard to incident and prevalent rates of delirium for African American patients in the ICU (22). Confusion assessment method for the ICU scores were not reliably collected in our data and are heterogeneously collected in diverse ICU settings. Therefore, we did not report this information. Importantly, we believe the clinical assessment of RASS more appropriately identifies our outcome of interest of deep sedation (3, 4). Last, race, as documented in the electronic health record, is ideally entered as the race with which a patient identifies. We know that is not always necessarily the case, and race may be misassigned by hospital staff (23). This is especially true in the ICU setting, given the limitations in communicating with patients who are sedated and mechanically ventilated. Specific information on sedative dosing, especially cumulative dosing is important to explore in future studies. Considering our cohort, we did have a significantly higher number of females patients in the Black cohort vs. the White cohort. Male patients may have augmented renal clearance, and therefore they may be a naturally increased prevalence of rapid drug clearance in the Black cohort. Furthermore, we do not control specifically for kidney injury or the use of renal replacement therapy in the

first 48 hours, which may impact this consideration. Sophisticated analyses of sedation consumption in critically ill White and Black patients warrants further dedicated analyses.

CONCLUSIONS

Black race was associated with a higher proportion of time in deep sedation during the first 48 hours of mechanical ventilation across diverse ICUs. Future work is needed to determine the clinical significance of these findings. There is a specific need to test associations of length of time in early deep sedation with clinical outcomes to elucidate potential mechanisms for outcomes disparities among Black patients with respiratory failure.

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Drs. Ramadurai, Kohn, and Kerlin were involved in study conceptualization and design. Ms. Scott was involved in data collection. Drs. Ramadurai and Kohn were involved in statistical analysis. Drs. Ramadurai, Kohn, Hart, and Kerlin were involved in interpretation of results. Dr. Ramadurai was involved in ultimately responsible for content of article as presented. All authors were involved in article preparation and approval of final version of the article.

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