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Association Between Postoperative Delirium and Long-Term Subjective Cognitive Decline in Elderly Cardiac Surgery Patients: A Secondary Analysis of the MINDDS Trial

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Abstract

Objectives: This study aimed to evaluate whether a measure of subjective cognitive decline (SCD), the PROMIS Applied Cognition-Abilities questionnaire, was associated with postoperative delirium. It was hypothesized that delirium during the surgical hospitalization would be associated with a decrease in subjective cognition up to six months after cardiac surgery.

Design: This was a secondary analysis of data from the Minimizing Intensive Care Unit Neurological Dysfunction with Dexmedetomidine-induced Sleep (MINDDS) randomized, placebo-controlled, parallel-arm, superiority trial.

Setting: Data from patients recruited between March 2017 and February 2022 at a tertiary medical center in Boston, Massachusetts, was analyzed in February 2023.

Participants: Data from 337 patients aged 60 years or older who underwent cardiac surgery with cardiopulmonary bypass were included.

Interventions: Patients were assessed preoperatively, and postoperatively at 30, 90 and 180-days using the subjective PROMIS Applied Cognition-Abilities and telephonic Montreal Cognitive Assessment.

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*Supplementary Appendix 1 includes a full list of MINDDS Study Team members

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Measurement and Main Results: Postoperative delirium occurred within three days in 39 (11.6%) participants. After adjusting for baseline function, participants who developed postoperative delirium self-reported worse cognitive function (mean difference [MD] −2.64 [95% CI: −5.25, −0.04]; p=0.047) up to 180 days after surgery as compared to non-delirious patients. This finding was consistent with those obtained from objective t-MoCA assessments (MD −0.77 [95% CI: −1.49, −0.04]; p=0.04).

Conclusions: In this cohort of elderly patients undergoing cardiac surgery, in-hospital delirium was associated with SCD up to 180 days after surgery. This finding suggests that measures of SCD may enable population-level insights into the burden of cognitive decline associated with postoperative delirium.

Keywords

delirium; subjective cognitive decline; cognition; postoperative; cardiac surgery

Introduction

Postoperative neurocognitive disorders[1] are defined as cognitive decline diagnosed up to 12 months postoperatively, and are common after cardiac surgery[2, 3]. Objective cognitive assessments, including in-person[2-4] and telephonic assessments[5-7], are typically used to track cognitive trajectory after surgery. However, these objective assessments are challenging to administer at scale to enable population-level insights into perioperative neurocognitive disorders.

Subjective cognitive decline (SCD), the self-reported worsening of cognitive performance[8], has been associated with an increased risk of cognitive decline[9, 10], and Alzheimer's disease biomarker abnormalities[11]. Compared to objective assessments of cognitive function, SCD measures may provide population-level data into cognitive trajectories associated with surgery because they are often easier to implement. Previous studies have reported associations between postoperative delirium and worse cognitive recovery using objective cognitive assessments[4, 12]. However, it is not yet clear whether measures of SCD can be used to characterize the cognitive trajectory associated with postoperative delirium.

The National Institutes of Health Patient-Reported Outcomes Measurement Information System (PROMIS®) Applied Cognition is a measure of SCD that relies upon participants self-assessment using a validated questionnaire[13]. Therefore, this study aimed to evaluate whether postoperative delirium was associated with a worse SCD trajectory up to six months after cardiac surgery. It was hypothesized that patients who experienced delirium would self-report worsening cognitive decline up to 180 days after surgery.

Methods

Study Design and Participants

This was a secondary analysis of data from the Minimizing Intensive Care Unit (ICU) Neurological Dysfunction with Dexmedetomidine-induced Sleep (MINDDS) clinical trial[14]. Briefly, the MINDDS trial was a randomized, placebo-controlled, double-blinded, single-

site, parallel-arm superiority trial. Patients aged 60 years or older, who underwent cardiac surgery with planned cardiopulmonary bypass and planned postoperative admission to the ICU for at least 24 hours, provided written informed consent and were randomized to receive either dexmedetomidine (1mcg/kg over 40 minutes) or placebo. The resulting sample size of the MINDDS parent trial was 394 patients in the modified intention-to-treat population. In this manuscript, data from 337 patients were available for analyses, including all of those in the modified intention-to-treat cohort for whom their postoperative delirium status could be evaluated (Supplementary Appendix 2). Specific details and results from the parent trial have been previously reported[15].

Study Measures and Outcomes

Postoperative delirium, the exposure of interest for this analysis, was assessed twice daily using the Confusion Assessment Method (CAM). The CAM is a validated instrument that identifies delirium based on acute onset and fluctuating course, inattention, and the presence of either disorganized thinking or an altered level of consciousness[16]. In this study delirium was defined as present if it occurred at any time during the first three days after surgery, using in-person assessments with trained raters.

The primary outcome in the present study, subjective cognition, was assessed using the PROMIS Applied Cognition-Abilities 8a Short Form. This tool was developed using item response theory to assess self-perceptions of cognition in the past seven days[17]. On a scale of 1 (not at all) to 5 (very much), patients were asked to rate themselves on eight questions which assess aspects of cognition including memory, thinking and concentration, among others. The total raw score which ranges from 0 to 40 was then converted to a T-score with a mean of 50 and a standard deviation of 10, with higher scores representing better self-perceived cognitive function. Cognition was measured at baseline, as well as at 30, 90 and 180 days after surgery. Presence of SCD as a binary variable, defined as a PROMIS Applied Cognition-Abilities score < 45, was assessed as a secondary outcome[18].

In addition to measures of SCD, the telephonic Montreal Cognitive Assessment (t-MoCA), often referred to as an abbreviated MoCA, was performed in order to obtain an objective measure of cognitive function as a secondary outcome. The t-MoCA is a validated cognitive screening test for the detection of mild cognitive impairment. It was developed by Nasreddine et al[19] and has a sensitivity of 90% and specificity of 100%. The t-MoCA ranges from 0 to 22 points, in order of increasing cognitive function. Previous studies have defined objective cognitive impairment as a t-MoCA ≤ 17[20].

Statistical Analysis

Data were summarized as mean ± standard deviation or median [interquartile range (IQR)] for continuous variables, and as frequency counts and proportions for categorical variables. Normality of continuous variables was assessed using a Shapiro-Wilk test and confirmed with a visual inspection of the data. Differences in baseline and surgical characteristics between patients who did and did not develop delirium were assessed using a chi-square test, t-test or Wilcoxon Rank Sum Test, depending on variable type and distribution.

Correlations between PROMIS Applied Cognition-Abilities and t-MoCA scores were assessed and reported using Pearson's correlation coefficients (r).

In order to assess the primary and secondary outcomes, generalized linear mixed effect models were specified with a gaussian distribution and identity link. In these models a random slope for each subject was included. The final models were adjusted for clinically relevant baseline characteristics and included age, sex, highest education level, PROMIS T-scores for pain interference and global physical function at baseline, treatment status (dexmedetomidine or placebo) and baseline cognitive status. Separate models were constructed for PROMIS Applied Cognition and t-MoCA scores, with results presented as the mean difference (MD) and its associated 95% confidence interval (CI). All analyses were conducted in SAS version 9.4 (SAS Institute Inc., Cary NC), with two-sided p-values less than 0.05 considered statistically significant. No imputation for missing data or adjustment for multiple testing was performed given the exploratory nature of this secondary analysis.

Role of the Sponsor

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Results

Baseline Characteristics

Of the 337 patients included in this analysis, 39 (11.6%) developed postoperative delirium within three days of surgery. Overall respondents were predominantly male with a median age of 68 years [IQR 64, 74], the majority of which reported a high level of educational attainment at enrollment (63.9% had a bachelor's degree or above). The median subjective (PROMIS Applied Cognition) and objective (t-MoCA) scores among all participants were 51.7 [IQR 46.8, 62.7] and 19.0 [17.0, 20.0], respectively. A statistically significant association between subjective and objective measures of cognition was observed at baseline ($r = 0.113$; $p = 0.04$). At baseline, 18.7% of the patients self-reported SCD and 25.5% screened positive for mild cognitive impairment using the objective t-MoCA.

Surgical and Crude Outcome Characteristics

Several differences were observed between the delirious and non-delirious patients at baseline. Patients who experienced delirium were older (72 [68, 77] vs 68 [63, 73]; $p < 0.001$), more commonly female (46.2% vs 23.5%; $p = 0.003$) and reported lower levels of cognition by both subjective and objective measures at baseline (Table 1). No statistically significant difference was observed between randomization strata.

Surgical characteristics and outcomes stratified by delirium groups are presented in Table 2. Interestingly, patients with delirium underwent longer periods of cardiopulmonary bypass as compared to non-delirious patients (148 [101, 191] vs 120 [92, 158], $p = 0.048$). Additionally, longer ICU and hospital stays were observed among patients with delirium. When considering cognition, patients with delirium reported lower PROMIS Applied

Cognition and t-MoCA scores at all time points. A similar observation was observed when considering the adjusted marginal mean cognitive scores, in which delirious patients reported consistently lower subjective and objective measures of cognition (Table 3; Figure 1).

Association Between Delirium Status and Neurocognition at Follow Up

A total of 253, 218 and 221 patients were contacted at 30, 90 and 180 days, respectively. Significant correlations between PROMIS Applied Cognition scores and t-MoCA were observed at all time points. This was most pronounced at 180 days ($r = 0.295$; $p < 0.001$), followed by 30 days ($r = 0.204$; $p = 0.001$) and 90 days ($r = 0.167$, $p = 0.01$).

Results of the models evaluating the association between postoperative delirium status and cognition at longer term follow up, conditional on the time point and baseline cognitive status, are reported in Table 4. In a model adjusted for timepoint and baseline cognition only, patients with delirium experienced a 3.04 point reduction (95% CI: −5.81, −0.27; $p = 0.03$) in the subjective PROMIS Applied Cognition as compared to non-delirious patients. These results were conserved in the final model after adjusting for baseline status (MD −2.64, 95% CI: −5.25, −0.04; $p = 0.047$).

Similar results were observed for the t-MoCA scores at follow up, in which patients with delirium reported lower objective cognitive scores at follow up both after adjusting for timepoint and baseline cognition (MD −0.88, 95% CI: −1.63, −0.14; $p = 0.02$), and in the fully adjusted models (MD −0.77, 95% CI: −1.49, −0.04; $p = 0.04$), as compared to non-delirious patients.

Discussion

In this study, several factors were associated with postoperative delirium including increased age, female sex, and worse physical and cognitive function at baseline. Importantly, postoperative delirium was associated with self-reported worsening of cognitive performance up to 180 days after surgery as compared to non-delirious patients. After adjusting for baseline cognitive performance, this finding persisted. This study also confirmed previously described associations between postoperative delirium and objective assessments of cognition using objective t-MoCA. Taken together, these results suggest that self-reported worsening of cognitive performance in patients older than 60 years may be used to estimate the burden of cognitive impairment associated with postoperative delirium.

Routine monitoring of cognitive function using a battery of tests can be time-consuming[21], and financially prohibitive[22]. Additionally, data from validated objective tests, as in the case of t-MoCA, may be confounded by learning effects that make it challenging to estimate the incidence of underlying cognitive impairment[23, 24]. Conversely, subjective measures are easier to administer, which makes them ideal for large-scale assessments, and may be used in the future to provide insight into population-level estimates. If obtained, population level estimates of SCD after surgery may enable clinicians to understand trends, associated risk factors and facilitate distribution of limited resources[25]. It may also indicate sensitivity

to later cognitive impairment, which may necessitate mandates for formal preoperative screening of at-risk patients[26, 27].

This study adds to the body of literature evaluating subjective and objective measures of cognition. Howland and colleagues previously reported a significant correlation between the PROMIS Applied Cognition-Abilities scores and the objective Mini Mental State Exam score ($r = 0.24$)[13]. In the present study, a similar correlation with the t-MoCA score was observed, which was most pronounced at the 180-day timepoint. It should be noted however that these correlations are quite modest in magnitude.

Despite these correlations, it is unclear whether SCD and objective cognitive assessments measure similar constructs. The PROMIS Applied Cognition-Abilities questionnaire comprises eight self-assessments of attention and memory[28]. In contrast, the t-MoCA assesses memory, attention, language, abstraction and orientation domains[29, 30]. However, both tools have been validated for assessing cognitive abilities, and are correlated to suggest they measure overlapping constructs.

Limitations

This study has several limitations, several of which are inherent to the study design of the current analysis within the context of a randomized controlled trial. This includes the possibility of residual confounding for nested cohort studies, as well as a missing data and a fixed sample size with only 39 delirious patients, potentially limiting the power of this secondary analysis. The loss to follow up was also higher in the parent trial than anticipated. It is unclear whether this missingness was related to their delirium or cognitive status, which may have limited the results we observed. Previous studies by our group have shown that the COVID-19 pandemic was associated with increased patient hesitancy[31] which also may have contributed to the loss to follow up in this trial. Additionally, the MINDDS trial was an interventional study aimed at reducing the intervention of delirium, with delirium assessments restricted to the first three days postoperatively. This implies that the incidence of postoperative delirium in our cohort may have been lowered by both the intervention and unassessed delirium occurring later during the hospital stay. Thus, although the findings described in this manuscript met our threshold for statistical significance, the effect sizes described may have been underestimated. Further limiting our interpretations for the present analysis, a single version of the t-MOCA was administered at four times to each study participant. Therefore, the resulting improvement in t-MOCA findings may have been secondary to a learning effect and should be interpreted in that context. Finally, the study cohort consisted of predominantly white patients enrolled from a single geographic region, potentially limiting the generalizability of these results.

Conclusion

In patients older than 60 years with low baseline risk of postoperative delirium admitted to the ICU after cardiac surgery and extubated within 12 hours of ICU admission, SCD may enable population-level insights into the burden of cognitive decline associated with postoperative delirium.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding Sources:

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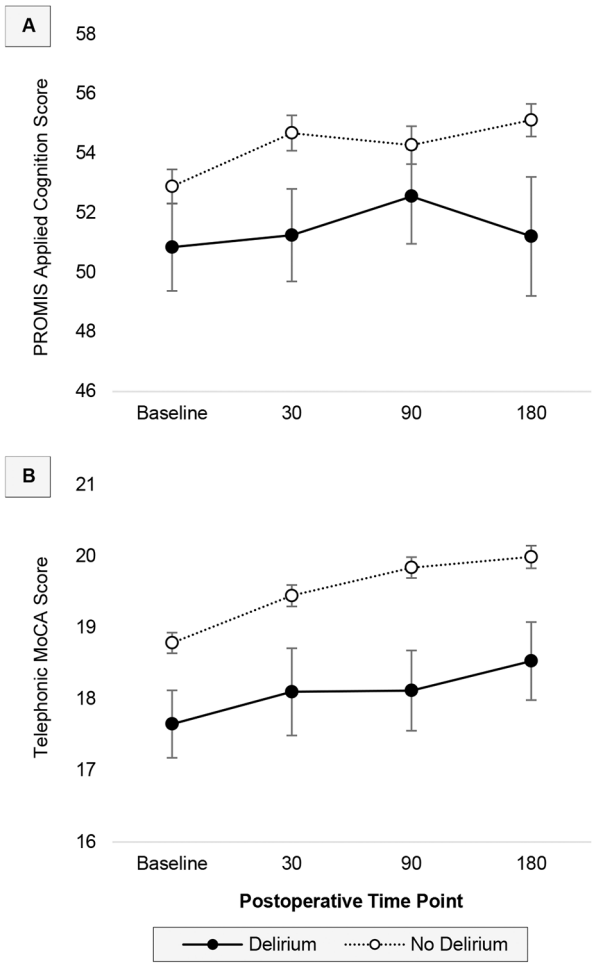

Figure 1.

Adjusted mean differences for the Telephonic Montreal Cognitive Assessment (t-MoCA) and Patient-Reported Outcomes Measurement Information System (PROMIS) Applied Cognition-Abilities scores at each timepoint, stratified by delirium status. Error bars represent the standard error of the estimate. Estimates have been adjusted for age, sex, highest education level, pain interference and global physical function at baseline, treatment status (dexmedetomidine or placebo), as well as the interaction with timepoint.

Table 1.

Participant Characteristics Stratified by Delirium Status

	Entire Cohort *N=337*	No Delirium *N=298*	Delirium[a] *N=39*	P-Value
Demographics				
Age, *years*	68 [64, 74]	68 [63, 73]	72 [68, 77]	< 0.001
Body Mass Index, kg/m^2	27.8 [24.8, 31.6]	27.8 [25.1, 31.5]	27.8 [24.3, 31.9]	0.89
Female Sex	88 (26.11)	70 (23.49)	18 (46.15)	0.002
White Race	249 (73.89)	289 (96.98)	39 (100.00)	0.61
Highest Level of Education[b]				<0.001
High School or Less	51 (15.18)	36 (12.12)	15 (38.46)	
Some College/Associate	70 (20.83)	65 (21.89)	5 (12.82)	
Degree				
Bachelor's Degree	101 (30.06)	92 (30.98)	9 (23.08)	
Master's or Doctorate Degree	114 (33.93)	104 (35.02)	10 (25.64)	
Comorbidities and Past Medical History				
Diabetes	76 (22.55)	67 (22.48)	9 (23.08)	0.93
Hypertension	262 (77.74)	229 (76.85)	33 (84.62)	0.27
Prior Myocardial Infarction	33 (9.79)	29 (9.73)	4 (10.26)	0.92
Previous Cardiac Intervention	106 (31.45)	90 (30.20)	16 (41.03)	0.17
Peripheral Arterial Disease	26 (7.72)	18 (6.04)	8 (20.51)	0.01
Cerebrovascular Disease	37 (10.98)	26 (8.72)	11 (28.21)	0.001
Liver Disease	15 (4.45)	15 (5.03)	0 (0)	0.23
Syncope	12 (3.56)	12 (4.03)	0 (0)	0.37
Sleep Apnea	15 (4.45)	63 (21.14)	10 (25.64)	0.52
Chronic Lung Disease	48 (14.24)	42 (14.09)	6 (15.38)	0.83
Smoking Status				0.045
Current Smoker	12 (3.56)	10 (3.36)	2 (5.13)	
Former Smoker	167 (49.55)	141 (47.32)	26 (66.67)	
Never Smoked	158 (46.88)	147 (49.33)	11 (28.21)	
Baseline Neurocognitive and PROMIS Scores				
Telephonic MoCA	19.0 [17.0, 20.0]	19.0 [18.0, 20.0]	18.0 [15.0, 20.0]	0.01
PROMIS Scores[c]				
Applied Cognition	51.7 [46.8, 62.7]	53.0 [46.8, 62.7]	50.6 [43.3, 56.8]	0.09
Global Health – Physical	50.8 [42.3, 57.7]	50.8 [44.9, 57.7]	44.9 [37.4, 50.8]	0.002
Global Health – Mental	56.0 [50.8, 62.5]	56.0 [50.8, 62.5]	50.8 [43.5, 59.0]	0.003
Physical Function	45.5 [40.1, 52.5]	46.4 [40.8, 59.7]	40.8 [35.5, 48.8]	0.002
Pain Interference	40.7 [40.7, 53.2]	40.7 [40.7, 53.2]	47.9 [40.7, 58.1]	0.06
Sleep Disturbance [d]	50.5 [43.8, 56.1]	50.5 [43.8, 56.1]	50.5 [41.1, 56.1]	0.68
Randomization Assignments				
Treatment				0.12

	Entire Cohort ***N=337***	**No Delirium** ***N=298***	**Delirium[a]** ***N=39***	**P-Value**
Placebo	177 (52.52)	152 (51.01)	25 (64.10)	
Dexmedetomidine	160 (47.48)	146 (48.99)	14 (35.90)	

Data is presented as median [quartile 1, quartile 3] or n (%) depending on variable type. Delirium is defined as present if it occurred within three days postoperatively following surgery.

[b] Education status is unknown for one individual.

[c] All PROMIS scores are translated to t-scores for reporting.

[d] Sleep disturbance was added after initiation of the trial, therefore this value is missing for twelve participants. *Abbreviations: MoCA (Montreal Cognitive Assessment), PROMIS (Patient-Reported Outcomes Measurement Information System)*

Table 2.

Surgical and Outcome Characteristics Stratified by Delirium Status

	Entire Cohort ***N=337***	**No Delirium** ***N=298***	**Delirium**[a] ***N=39***	**P-Value**
Surgical Information				
Cardiopulmonary Bypass Time, *minutes*	122 [93, 161]	120 [92, 158]	148 [101, 191]	0.048
Cross Clamp Time, *minutes*[b]	87 [69, 116]	86 [69, 115]	102 [69, 138]	0.19
Clinical Characteristics				
Length of Hospital Stay, *days*	6 [5, 7]	6 [5, 7]	7 [6, 9]	0.001
Length of ICU Stay, *hours*	25.2 [23.0, 40.0]	25.0 [23.0, 31.0]	34.0 [24.0, 70.0]	0.002
Total Ventilation Time, *hours*	5.00 [3.97, 6.93]	4.92 [3.92, 6.65]	7.18 [4.42, 8.85]	<0.001
Mortality Status				
30 Days	2 (0.59)	1 (0.34)	1 (2.56)	0.22
90 Days	3 (0.89)	1 (0.34)	2 (5.13)	0.003
180 Days	6 (1.78)	3 (1.01)	3 (7.69)	0.02
Neurocognitive Outcomes				
Number Assessed at Follow Up				
30 Days	253	232	21	---
90 Days	218	200	18	---
180 Days	221	203	18	---
Telephonic MoCA				
30 Days	20.0 [18.0, 21.0]	20.0 [18.0, 21.0]	19.5 [14.5, 21.0]	0.21
90 Days	20.0 [19.0, 21.0]	20.0 [19.0, 21.0]	19.0 [16.0, 21.0]	0.03
180 Days	21.0 [19.0, 22.0]	21.0 [20.0, 22.0]	19.0 [17.0, 21.0]	0.02
PROMIS Applied Cognition[c]				
30 Days	54.6 [47.7, 62.7]	54.6 [48.6, 62.7]	51.7 [45.1, 54.6]	0.02
90 Days	54.6 [48.6, 62.7]	54.6 [48.6, 62.7]	53.0 [45.1, 56.8]	0.26
180 Days	54.6 [49.5, 62.7]	54.6 [49.5, 62.7]	49.5 [45.9, 51.7]	0.01

Data is presented as median [quartile 1, quartile 3] or n (%) depending on variable type.

[a]Delirium is defined as present if it occurred within three days postoperatively following surgery.

[b]Cross clamp time was missing for one participant who did not have their aorta clamped.

[c]All PROMIS scores are translated to t-scores for reporting. *Abbreviations: MoCA (Montreal Cognitive Assessment), PROMIS (Patient-Reported Outcomes Measurement Information System), ICU (intensive care unit).*

Table 3.

Adjusted[a] Mean Cognitive Scores at Follow Up Stratified by Delirium Status

	Delirium[b]	No Delirium	Mean Difference Between Groups *(95% Confidence Interval)*	P-value
PROMIS Applied Cognition-Abilities				
Baseline Preoperatively	50.85	52.89	−2.04 (−5.07, 0.98)	0.19
30 days	51.25	54.68	−3.43 (−6.64, −0.23)	0.01
90 days	52.56	54.28	−1.72 (−5.06, 1.61)	0.31
180 days	51.21	55.12	−3.90 (−7.95, 0.14)	0.06
Telephonic MoCA				
Baseline Preoperatively	17.65	18.79	−1.14 (−2.11, −0.16)	0.02
30 days	18.10	19.45	−1.35 (−2.57, −0.12)	0.03
90 days	18.12	19.84	−1.72 (−2.87, −0.57)	0.003
180 days	18.53	19.99	−1.46 (−2.58, −0.33)	0.01

[a]Values represent the marginal mean values in a model adjusted for age, sex, highest education level, treatment status (dexmedetomidine or placebo), pain interference and global physical function at baseline.

[b]Delirium is defined as present if it occurred within three days postoperatively following surgery. *Abbreviations: MoCA (Montreal Cognitive Assessment), PROMIS (Patient-Reported Outcomes Measurement Information System)*

Table 4.

Association Between Delirium Status and Neurocognition Through Six Months Postoperatively

	Crude Model		Adjusted for Baseline Cognition		Adjusted Final Model[a]	
	Mean Difference *(95% Confidence Interval)*	**P-Value**	**Mean Difference *(95% Confidence Interval)***	**P-Value**	**Mean Difference *(95% Confidence Interval)***	**P-Value**
PROMIS Applied Cognition Models						
Postoperative Delirium	−4.32 (−7.39, −1.25)	0.01	−3.04 (−5.81, −0.27)	0.03	−2.64 (−5.25, −0.04)	0.047
Time						
30 Days	REFERENCE	---	REFERENCE	---	REFERENCE	---
90 Days	−0.29 (−1.39, 0.81)	0.60	−0.31 (−1.40, 0.78)	0.58	−0.29 (−1.38, 0.81)	0.61
180 Days	0.42 (−0.60, 1.44)	0.42	0.41 (−0.61, 1.42)	0.43	0.41 (−0.62, 1.43)	0.44
Baseline Cognition [b]	---	---	0.31 (0.20, 0.41)	<0.001	0.27 (0.16, 0.38)	<0.001
Telephonic MoCA Models						
Postoperative Delirium	−1.80 (−3.04, −0.56)	0.005	−0.88 (−1.63, −0.14)	0.02	−0.77 (−1.49, −0.04)	0.04
Time						
30 Days	REFERENCE	---	REFERENCE	---	REFERENCE	---
90 Days	0.37 (0.14, 0.61)	0.002	0.36 (0.12, 0.60)	0.003	0.36 (0.13, 0.60)	0.003
180 Days	0.56 (0.30, 0.83)	<0.001	0.55 (0.29, 0.81)	<0.001	0.54 (0.28, 0.80)	<0.001
Baseline Cognition [b]	---	---	0.60 (0.51, 0.69)	<0.001	0.58 (0.48, 0.68)	<0.001

[a]The final model has been adjusted for age, sex, highest education level, pain interference and global physical function at baseline, treatment status (dexmedetomidine or placebo), and baseline cognitive status. Beta estimates for additional model covariates are not presented.

[b]Models adjusted for baseline cognition include the preoperative PROMIS Applied Cognition T-Score or Telephonic MoCA (respectively, depending on outcome) value as a covariate. *Abbreviations: MoCA (Montreal Cognitive Assessment), PROMIS (Patient-Reported Outcomes Measurement Information System)*