NOVEL PERIOPERATIVE RISK FACTORS AND THEIR CONTRIBUTION TO POSTOPERATIVE DELIRIUM

by

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Background

According to the World Health Organization (WHO), the number of people aged 60 years or older will rise from 900 million to 2 billion between 2015 and 2050.(1) In the United States, the Centers for Disease Control and Prevention (CDC) reported more than 19 millions anesthetics were administered to patients aged 65 or older in 2010.(2) Surgical procedures under general anesthesia are expected to increase in the future in geriatric patients.(3) Older patients have higher rates of postoperative morbidity and mortality when compared to younger adults.(4) Improvements to the perioperative care of older patients may benefit clinical outcomes.

Delirium is a clinical outcome that may be modified by perioperative care practices. It is defined as an acute brain dysfunction characterized by disturbances in attention, awareness, and cognition.(5) Delirium is associated with an increased risk of dementia.(6, 7) It may also a trigger a cascade of events that culminate in higher healthcare costs, loss of independence, increased morbidity, and mortality.(8) The incidence of delirium, which is already high in older patients, is further increased after surgery.(9, 10)

Postoperative delirium (POD) is defined as the new onset delirium within 7 days of surgery.(11) Pathophysiological mechanisms underlying POD are actively been investigated.(12, 13) However, POD has been associated with numerous risk factors including baseline cognitive impairment and frailty.(14-17) Recent studies have made clear that intraoperative electroencephalography (EEG) dynamics such as burst suppression are associated with delirium. Thus, EEG-derived features may aid interpretable machine-learning based strategies to identify patients at risk of POD.

It is presently unclear whether the EEG burst-suppression in patients that develop delirium is a readout of previously reported delirium risk factors versus whether it represents an independent delirium risk factor for delirium. This distinction is clinically relevant. Therefore, in our first study, we investigated whether burst-suppression mediates the effects of known delirium risk factors on postoperative delirium. In our second study, we further investigated the relationship between frailty, postoperative delirium and mortality.

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ANESTHESIOLOGY

Electroencephalogram Burst-suppression during Cardiopulmonary Bypass in Elderly Patients Mediates Postoperative Delirium

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Associations between intraoperative burst suppression and postoperative delirium have been reported.
- The causal significance of these associations is unknown.

What This Article Tells Us That Is New

- In a retrospective observational substudy of 159 patients undergoing cardiac surgery, there is evidence that burst suppression during cardiopulmonary bypass mediates the effect of physical function, temperature during cardiopulmonary bypass, and intraoperative electroencephalographic alpha power on postoperative delirium. Delirium was also associated with decreased broadband power in the intraoperative electroencephalogram.

ABSTRACT

Background: Intraoperative burst-suppression is associated with postoperative delirium. Whether this association is causal remains unclear. Therefore, the authors investigated whether burst-suppression during cardiopulmonary bypass (CPB) mediates the effects of known delirium risk factors on postoperative delirium.

Methods: This was a retrospective cohort observational substudy of the Minimizing ICU [intensive care unit] Neurological Dysfunction with Dexmedetomidine-induced Sleep (MINDDS) trial. The authors analyzed data from patients more than 60 yr old undergoing cardiac surgery (n = 159). Univariate and multivariable regression analyses were performed to assess for associations and enable causal inference. Delirium risk factors were evaluated using the abbreviated Montreal Cognitive Assessment and Patient-Reported Outcomes Measurement Information System questionnaires for applied cognition, physical function, global health, sleep, and pain. The authors also analyzed electroencephalogram data (n = 141).

Results: The incidence of delirium in patients with CPB burst-suppression was 25% (15 of 60) compared with 6% (5 of 81) in patients without CPB burst-suppression. In univariate analyses, age (odds ratio, 1.08 [95% CI, 1.03 to 1.14]; $P = 0.002$), lowest CPB temperature (odds ratio, 0.79 [0.66 to 0.94]; $P = 0.010$), alpha power (odds ratio, 0.65 [0.54 to 0.80]; $P < 0.001$), and physical function (odds ratio, 0.95 [0.91 to 0.98]; $P = 0.007$) were associated with CPB burst-suppression. In separate univariate analyses, age (odds ratio, 1.09 [1.02 to 1.16]; $P = 0.009$), abbreviated Montreal Cognitive Assessment (odds ratio, 0.80 [0.66 to 0.97]; $P = 0.024$), alpha power (odds ratio, 0.75 [0.59 to 0.96]; $P = 0.025$), and CPB burst-suppression (odds ratio, 3.79 [1.5 to 9.6]; $P = 0.005$) were associated with delirium. However, only physical function (odds ratio, 0.96 [0.91 to 0.99]; $P = 0.044$), lowest CPB temperature (odds ratio, 0.73 [0.58 to 0.88]; $P = 0.003$), and electroencephalogram alpha power (odds ratio, 0.61 [0.47 to 0.76]; $P < 0.001$) were retained as predictors in the burst-suppression multivariable model. Burst-suppression (odds ratio, 4.1 [1.5 to 13.7]; $P = 0.012$) and age (odds ratio, 1.07 [0.99 to 1.15]; $P = 0.090$) were retained as predictors in the delirium multivariable model. Delirium was associated with decreased electroencephalogram power from 6.8 to 24.4 Hertz.

Conclusions: The inference from the present study is that CPB burst-suppression mediates the effects of physical function, lowest CPB temperature, and electroencephalogram alpha power on delirium.

(ANESTHESIOLOGY 2020; XXX:00–00)

Delirium is an acute brain dysfunction characterized by disturbances in attention, awareness, and cognition.[1] Normal aging,[2] poor physical function,[3,4] preexisting cognitive impairment,[5,6] sedative drugs,[7] sleep disturbance,[8] and inflammation[9] are risk factors that predispose patients to delirium. Although previously reported associations between delirium and increased mortality may not be causal,[10] delirium remains a leading cause of preventable

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morbidity in hospitalized elderly patients.[10,11] Thus, strategies to reduce the incidence of delirium and identify patients at risk for delirium are needed.

Burst-suppression during general anesthesia is associated with postoperative delirium.[12–14] Burst-suppression consists of alternations between isoelectricity and brief bursts of electrical activity.[15] Burst-suppression can be induced by anesthetic drugs that significantly modulate γ-aminobutyric acid type A receptors. Although sometimes induced intentionally for therapeutic purposes to treat refractory status epilepticus or increased intracranial pressure,[16,17] burst-suppression is generally considered potentially harmful and to be avoided. Whether burst-suppression is a modifiable risk factor for delirium *versus* merely an epiphenomenon or downstream readout for other factors that cause delirium is an open question.

If burst-suppression contributes causally to delirium, this argues for anesthetic protocols to reduce the incidence of intraoperative burst-suppression. Conversely, a noncausal association would argue for anesthetic protocols to identify patients with intraoperative burst-suppression for preemptive geriatric consultation. In a recent investigation, we found that patients with intraoperative burst-suppression during cardiopulmonary bypass (CPB) exhibited decreased alpha and beta oscillation power compared with age-matched control patients.[18] This finding suggests that patients exhibiting burst-suppression at age-adjusted anesthetic concentrations are neurobiologically distinct. Consistent with this finding, an electroencephalogram-guided anesthetic protocol reduced the incidence of intraoperative burst-suppression but not postoperative delirium.[19] Thus, the association between drug-induced intraoperative electroencephalogram burst-suppression and delirium in noncritically ill patients may not be entirely causal.

In this study we investigated associations between delirium risk factors, electroencephalogram burst-suppression during CPB, and postoperative delirium. We analyzed the electroencephalogram for burst-suppression during CPB, a period with stable and controlled anesthetic and physiologic management. Decreased alpha power has been associated with burst-suppression during CPB[18] and cognitive impairment.[20,21] Cognitive impairment has also been associated with postoperative delirium.[5,6] We hypothesized that preexisting cognitive impairment accounts for electroencephalogram burst-suppression during CPB. We also hypothesized that electroencephalogram burst-suppression during CPB mediates the effect of cognitive impairment on delirium.

Materials and Methods

Patient Selection and Data Collection

Ethics Statement. The Partners Human Research Committee approved this research study (Institutional Review Board 20168000742). This is a substudy of the ongoing Minimizing ICU Neurologic Dysfunction with Dexmedetomidine-induced Sleep (MINDDS) trial.[22] The MINDDS trial is a 370-patient block-randomized, placebo-controlled, double-blinded, single-site, parallel-arm superiority trial of a sleep-inducing dose of dexmedetomidine for delirium prevention in elderly patients undergoing major cardiac surgery. For this substudy, data from eligible MINDDS trial patients who underwent preoperative assessments and had intraoperative electroencephalogram recordings were analyzed. All participants provided written informed consent.

Study Population. Study details for the MINDDS trial, including inclusion and exclusion criteria, have previously been published.[22] Study eligibility criteria were age at or above 60 years, scheduled for a cardiac surgical procedure with CPB, planned postoperative admission to the intensive care unit for at least 24 h, and scheduled same-day surgical admission. Study exclusion criteria were blindness, deafness, inability to speak English, more than 2 days of ICU admission in the month preceding the current surgical procedure, renal and liver failure requiring dialysis or Child-Pugh score greater than 5, anticipated follow-up difficulties, previous cardiac surgery within 1 yr of surgical procedure, allergy to dexmedetomidine, chronic therapy with benzodiazepines or antipsychotics, severe neurologic deficit, and surgical procedure requiring total circulatory arrest. Patients scheduled for a second surgical procedure during their hospital stay or postoperative intubation more than 12 h were dropped from the study. Data from 159 patients were analyzed in this prespecified substudy: 117 patients were followed up in the MINDDS trial, 7 patients withdrew consent for MINDDS trial long-term follow-up after surgery, 18 patients met objective drop criteria for MINDDS trial long-term follow-up, and 17 patients did not consent to be randomized into the MINDDS trial.

Data Collection. Patients underwent a baseline prerandomization assessment for study inclusion and exclusion criteria. Subjects were recruited and data collected between March 2017 and February 2019. We evaluated baseline cognitive function using the abbreviated Montreal Cognitive Assessment, physical function with the Patient-Reported Outcomes Measurement Information System SF v2.0-Physical function 8b, general health with the Patient-Reported Outcomes Measurement Information System SF v1.2-Global Health, pain with the Patient-Reported Outcomes Measurement Information System SF v1.0-Pain Interference 8a, applied cognition with the Patient-Reported Outcomes Measurement Information System v2.0-Applied Cognition Abilities 8a, and sleep quality with the Patient-Reported Outcomes Measurement Information System v1.0-Sleep Disturbance 4A. We also screened for delirium during the prerandomization assessment using the 3-min Confusion Assessment Method.

Patient-Reported Outcomes Measurement Information System measures were normalized to a standardized

T-distribution (https://www.assessmentcenter.net/ac_scoringservice; accessed March 31, 2019). The T-score mean for Patient-Reported Outcomes Measurement Information System questionnaires is 50 for the population, with SD of 10. Higher scores indicate more of the concept being measured. This could be a desirable or undesirable outcome, depending on the concept being measured (*i.e.*, higher scores for physical function is desirable while higher scores for pain or sleep disturbance is undesirable). None of the study patients screened positive for delirium during the baseline assessments. Comorbid conditions were extracted from the history and physical notes that were documented during the presurgical planning visit.

We recorded electroencephalogram data using Sedline monitor (Masimo Inc, USA). Sedtrace electrode arrays were placed on the forehead at approximately Fp1, Fp2, F7, and F8, the ground electrode at approximately Fpz, and the reference electrode approximately 1 cm above Fpz. Data were recorded with a preamplifier bandwidth of 0.5 to 92 Hertz, a sampling rate of 250 Hertz, with 16-bit, 29 nano Volts resolution. Electrode impedance was maintained at less than 5kΩ in each channel. General anesthesia was induced with an intravenous induction agent, followed by maintenance with isoflurane. We selected electroencephalogram data segments using information from the electronic medical record and spectral analysis of the electroencephalogram. For each patient, we carefully selected 2-min electroencephalogram segments that represented the maintenance phase of general anesthesia during surgery. The data were selected from a period at least 15 min after the initial induction bolus of the intravenous hypnotic, while the expired concentration of isoflurane was stable and before the onset of CPB. We visually inspected the selected segments in both the time and spectral domains to ensure data quality. These data have not been reported in any previous publication.

Burst-suppression Analysis. We manually identified patients who exhibited burst-suppression during CPB by analyzing electroencephalogram data in the spectral and time-series domain. Two independent anesthesiologists (J.P., O.A.) identified periods of burst-suppression defined as the presence of at least three consecutive suppression events within 60-s periods during CPB. Only cases that both evaluators agreed upon were formally coded as burst suppression events. We used complete cases analysis (n = 141).

Postoperative Delirium Analysis. Patients were screened for postoperative delirium twice daily (before midday and past midday with at least 6 h between tests) beginning on postoperative day 1 using the long version of the Confusion Assessment Method, until postoperative day 3. Delirium was also assessed with a structured chart review beginning on postoperative day 1 until postoperative day 3 by performing a text search for the diagnosis of *delirium* or *delirious* in the medical record.

Spectral Analysis. We computed multitaper spectral estimates using the Chronux Matlab toolbox with the following parameters: window length T = 2 s without overlap, time-bandwidth product TW = 3, number of tapers K = 5. We equally weighted the signals from Fp1, Fp2, F7, and F8 channels.

Bias. Selection bias was managed by analyzing data from all patients who were sequentially enrolled in the MINDDS study until the sample size for this substudy was reached. Misclassification was reduced by clearly defining exposures (burst-suppression during CPB) and outcomes (delirium). Data collection with the aid of standardized clinical tools (abbreviated Montreal Cognitive Assessment, Patient-Reported Outcomes Measurement Information System Health Measures, and Confusion Assessment Method) helped to minimize recall bias. However, the nature of our investigation does not preclude bias introduced by unknown or unmeasured confounders.

Statistical Methods

Data and statistical analyses plans were defined and written after the data were accessed. Continuous variables are presented as median [quartile 1 (25th percentile) to quartile 3 (75th percentile)] and categorical variables as frequency (percentage). We used the Mann–Whitney *U* test for associations between continuous and categorical variables, and the Fisher exact test for associations among categorical variables. All *P* values were computed based on the two-sided tests at significance level of 0.05. In some cases, multiple testing was corrected using false discovery rate. Significance was declared if false discovery rate < 0.05.

Power Analysis. A primary objective of this study was to detect a difference in mean preoperative cognitive scores between burst-suppression and no-burst-suppression patient groups. We assumed a sampling ratio (burst-suppression/no burst-suppression) during CPB in major cardiac surgery of 50%,[18] a reduction in abbreviated Montreal Cognitive Assessment score of 1.5 in the burst-suppression group, and an abbreviated Montreal Cognitive Assessment SD of 2.5. Based on type I error of 0.05, and power of 0.90, a total of 132 patients was expected to enable detection of this difference using a two-sample *t* test. We assumed approximately 20% data loss as a result of electroencephalogram poor quality and incomplete recordings and thus assumed our n of 159 to be adequate.

Electroencephalogram Analysis. We manually matched patients by actual age (± 2 yr) and abbreviated Montreal Cognitive Assessment (± 3 points) score using a one to one matching criteria. An empirical bootstrap approach was used to enable statistical inferences. First, we bootstrapped the estimates of each nonoverlapping window. Next, we computed a median of the bootstrapped estimates at the subject level and then computed the group median of this estimate. We computed the median difference between groups and then iterated the above procedure 5,000 times to obtain a distribution of the median difference between groups. We computed the 99% CI of this distribution. We

defined our threshold for statistical significance as when the upper and lower CI of the median difference distribution did not border zero over a contiguous frequency range greater than 2 bandwidths (2W).

Univariate Linear Regression Analysis. In separate linear regression analyses, we estimated the association between abbreviated Montreal Cognitive Assessment (using continuity correction) and the following delirium risk factors: age, American Society of Anesthesiologists (ASA) Physical Status (using continuity correction), education (more than high-school education categorized), applied cognition (Patient-Reported Outcomes Measurement Information System Cognition), physical function (Patient-Reported Outcomes Measurement Information System Physical Function), global health (Patient-Reported Outcomes Measurement Information System Global Health Physical and Mental), pain (Patient-Reported Outcomes Measurement Information System Pain), sleep (Patient-Reported Outcomes Measurement Information System Sleep), alpha power, and burst-suppression during CPB. Regression models were constructed in R (RStudio Inc, USA, version 1.1.453).

Univariate Logistic Regression Analysis. In separate logistic regression analyses, we estimated the association between burst-suppression during CPB and the following delirium risk factors: age, ASA Physical Status, abbreviated Montreal Cognitive Assessment, applied cognition (Patient-Reported Outcomes Measurement Information System Cognition), physical function (Patient-Reported Outcomes Measurement Information System Physical Function), global health (Patient-Reported Outcomes Measurement Information System Global Health Physical and Mental), pain (Patient-Reported Outcomes Measurement Information System Pain), sleep (Patient-Reported Outcomes Measurement Information System Sleep), alpha power, length of CPB, and lowest temperature during CPB. We also estimated the association between delirium and the same predictors as above including an analysis for the predictor burst-suppression during CPB. Regression models were constructed in R (RStudio Inc, version 1.1.453).

Causal/Mediational Inference Analysis. The analysis of potential underlying causal mechanisms suggested fitting separate multivariable logistic regression models for the dependent variables: burst-suppression during CPB and delirium. In the model for burst-suppression, the predictors were age, ASA Physical Status, abbreviated Montreal Cognitive Assessment, Patient-Reported Outcomes Measurement Information System Physical, Patient-Reported Outcomes Measurement Information System Global Mental Health, Patient-Reported Outcomes Measurement Information System Pain, Patient-Reported Outcomes Measurement Information System Cognition, Patient-Reported Outcomes Measurement Information System Sleep, alpha power, CPB length, and lowest temperature during CPB. In the model for delirium, the same predictors were analyzed with the addition of burst-suppression. In both models, a backward elimination algorithm was applied to the predictors. Only predictor terms that remained after backward elimination using a $P < 0.1$ significance threshold were included in the final model. These analyses were performed with SAS statistical software (SAS Institute Inc, USA, version 9.4). The hypothetical underlying causal model that guided our data analysis strategy is illustrated in figure 1. This figure makes clear that we are testing the hypothesis that burst-suppression partly mediates the hypothetical causal effects of the exogenous variables (age, ASA Physical Status, abbreviated Montreal Cognitive Assessment, Patient-Reported Outcomes Measurement Information System measures, alpha power, CPB measures) on delirium. However, we are also positing the possibility of additional direct effects of the exogenous variables on delirium additive to their indirect effects *via* burst-suppression, as indicated by the direct arrows from exogenous variables to delirium. The age variable was the only exogenous variable that had largely the role of a potential confounding covariate rather than being of direct substantive interest in this study as the other predictors were. No modifier effects were tested (*i.e.*, no interactions among predictors).

Results

Patient Characteristics Stratified by Burst-suppression and Delirium

Data from 159 patients were analyzed in this manuscript. Patient characteristics are summarized in supplementary material (Supplemental Digital Content, table 1, http://links.lww.com/ALN/C365). Electroencephalogram data of 18 subjects could not be analyzed for burst-suppression because of poor quality or incomplete data capture throughout CPB. There were 23 patients who screened positive for delirium in our study cohort: 18 of the 117 MINDDS trial patients (16 from assessments, 2 chart review), 1 of the 7 patients who withdrew consent for MINDDS trial long term follow-up (1 from assessments, none from chart review), 3 of the 18 patients who met objective drop criteria for MINDDS trial long-term follow-up (none from assessments, 3 from chart review), and 1 of the 17 patients who did not consent to be randomized into the MINDDS trial (none from assessments, 1 from chart review). These data are summarized in the Supplemental Digital Content, table 2 (http://links.lww.com/ALN/C366). The characteristics of patients with complete electroencephalogram data stratified by burst-suppression and delirium are summarized in table 1 and Supplemental Digital Content table 3 (http://links.lww.com/ALN/C367), respectively. Patient comorbidities are summarized in Supplemental Digital Content, tables 4 (http://links.lww.com/ALN/C368) and 5 (http://links.lww.com/ALN/C369).

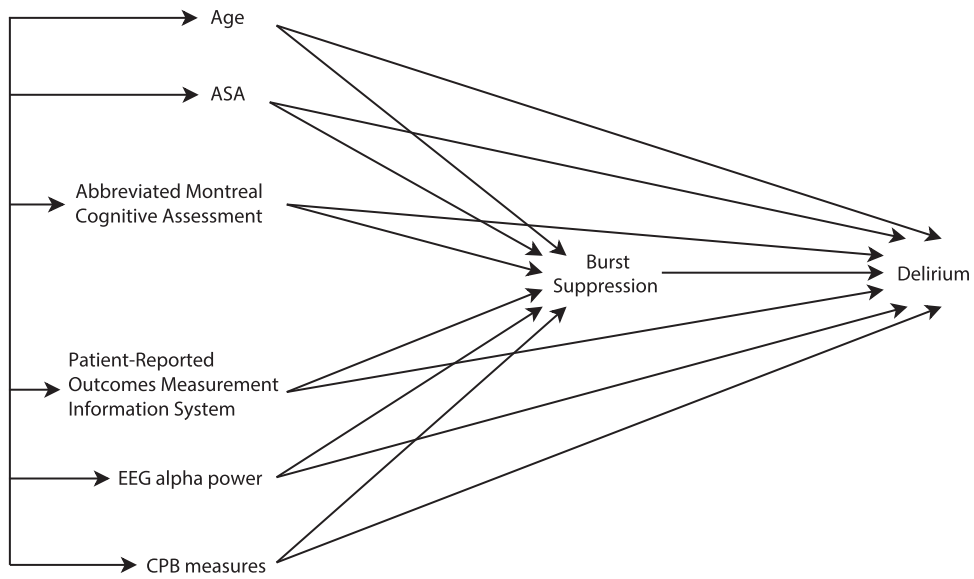

Fig. 1. Initial hypothetical causal model. Burst-suppression during cardiopulmonary bypass was hypothesized to mediate the association between known delirium risk factors and delirium. However, the initial model also allowed for the possibility of direct effects of the risk factors on delirium, in addition to, or instead of, the indirect, mediational effect of burst-suppression. Patient-Reported Outcomes Measurement Information System measures included applied cognition, physical function, global health, pain, and sleep. Cardiopulmonary bypass (CPB) measures included duration of CPB and lowest temperature during CPB. *Straight arrows* indicate causal effects; *double-headed arrows* connecting exogenous variables on the left indicate correlations not explicated in the model. ASA, American Society of Anesthesiologists Physical Status; EEG, electroencephalogram.

Univariate Analyses of Independent Associations

Age, Education, and Alpha Power Were Independently Associated with the Abbreviated Montreal Cognitive Assessment. We found significant independent associations with abbreviated Montreal Cognitive Assessment for age, education, and intraoperative alpha power (Supplemental Digital Content, table 6, http://links.lww.com/ALN/C370). The patient's predicted abbreviated Montreal Cognitive Assessment score decreased by 0.087 points for each year increase in age (false discovery rate $P = 0.008$). Predicted abbreviated Montreal Cognitive Assessment score increased by 1.096 points if patients were formally educated beyond high school education (false discovery rate $P = 0.014$). High school education was coded a 1 for at least a high school education and 0 for less than a high school education. Similarly, abbreviated Montreal Cognitive Assessment score increased 0.155 points for each decibel increase in intraoperative alpha power (false discovery rate $P = 0.033$).

Age, Physical Function Scores, Alpha Power, and Lowest Temperature during Cardiopulmonary Bypass Were Independently Associated with Burst-suppression during CPB. We found significant independent associations with the incidence of intraoperative burst-suppression during CPB for age, Patient-Reported Outcomes Measurement Information System Physical Function, Patient-Reported Outcomes Measurement Information System Global Health Physical, intraoperative alpha power, and lowest temperature during CPB. The odds of burst-suppression during CPB increased by 8% (odds ratio, 1.08 [95% CI, 1.03 to 1.14]; false discovery rate $P = 0.006$) for each year increase in age. The odds of burst-suppression during CPB decreased by 5% (odds ratio, 0.95 [0.91 to 0.98]; false discovery rate $P = 0.020$) for every T-score increase in Patient-Reported Outcomes Measurement Information System Physical Function. Similarly, the odds of burst-suppression during CPB decreased by 5% (odds ratio, 0.95 [0.92 to 0.99]; false discovery rate $P = 0.021$) for every T-score increase in Patient-Reported Outcomes Measurement Information System Global Health Physical Function. The odds of burst-suppression during CPB decreased by 35% (odds ratio, 0.65 [0.54 to 0.80]; false discovery rate $P < 0.001$) for each decibel increase in electroencephalogram alpha power. Finally, the odds of burst-suppression during CPB decreased by 21% (odds ratio, 0.79 [0.66 to 0.94]; false discovery rate $P = 0.024$) for each degree increase in lowest temperature during CPB. These data are summarized in Supplemental Digital Content, table 7 (http://links.lww.com/ALN/C371).

Age, Abbreviated Montreal Cognitive Assessment, Alpha Power, and Burst-suppression during Cardiopulmonary Bypass Were Independently Associated with Delirium. We found significant independent associations for age, abbreviated Montreal

Table 1. Patients Characteristics with Complete Electroencephalogram Data, Stratified by Burst Suppression

Burst Suppression	No Burst Suppression (n = 81)	Burst Suppression (n = 60)	*P* Value	False Discovery Rate *P* Value
Age, median [quartile 1 to quartile 3]	67 [64 to 73]	73 [68 to 78]	0.001	0.007
ASA Physical Status, n/total (%)			0.667	0.788
II	4/81 (5)	2/60 (3)		
III	57/81 (70)	39/60 (65)		
IV	20/81 (25)	19/60 (32)		
Abbreviated Montreal Cognitive Assessment, median [quartile 1 to quartile 3]	19 [17 to 20]	19 [17 to 20]	0.965	0.965
Patient-Reported Outcomes Measurement Information System Physical, median [quartile 1 to quartile 3]	48 [41 to 60]	43 [39 to 49]	0.007	0.018
Patient-Reported Outcomes Measurement Information System Global Health Physical, median [quartile 1 to quartile 3]	50 [43 to 55]	46 [38 to 51]	0.009	0.020
Patient-Reported Outcomes Measurement Information System Global Health Mental, median [quartile 1 to quartile 3]	56 [50 to 62]	54 [49 to 61]	0.541	0.703
Patient-Reported Outcomes Measurement Information System Pain, median [quartile 1 to quartile 3]	41 [41 to 52]	41 [41 to 55]	0.158	0.228
Patient-Reported Outcomes Measurement Information System Cognition, median [quartile 1 to quartile 3]	61 [51 to 61]	51 [51 to 61]	0.120	0.195
Patient-Reported Outcomes Measurement Information System Sleep, median [quartile 1 to quartile 3]	50 [44 to 56]	50 [44 to 57]	0.750	0.813
Alpha power, median [quartile 1 to quartile 3]	2.84 [1.85 to 6.54]	1.06 [0.68 to 2.22]	< 0.001	< 0.001
CPB length, median [quartile 1 to quartile 3]	113 [93 to 148]	133 [105 to 188]	0.028	0.052
Lowest CPB temperature, median [quartile 1 to quartile 3]	34.1 [33.7 to 34.5]	33.8 [31.2 to 34.3]	0.005	0.016
Delirium, n/total (%)	5/81 (25)	15/60 (75)	0.003	0.013

ASA, American Society of Anesthesiologists; CPB, cardiopulmonary bypass.

Cognitive Assessment, alpha power, and burst-suppression during CPB with delirium. The odds of delirium increased by 9% (odds ratio, 1.09 [1.02 to 1.16]; uncorrected $P = 0.009$) for each year increase in age. The odds of delirium decreased by 20% (odds ratio, 0.80 [0.66 to 0.97]; uncorrected $P = 0.024$) for each point increase in abbreviated Montreal Cognitive Assessment score. The odds of delirium decreased by 25% (odds ratio, 0.75 [0.59 to 0.96]; uncorrected $P = 0.025$) for each decibel increase in electroencephalogram alpha power. The odds of delirium increased by 279% (odds ratio, 3.79 [1.50 to 9.60]; uncorrected $P = 0.005$) in patients with burst-suppression during CPB. These findings did not meet our threshold for statistical significance after correction for multiple comparisons (Supplemental Digital Content, table 8, http://links.lww.com/ALN/C372).

Multivariable Logistic Regression Models

Alpha Power, Lowest Temperature during Cardiopulmonary Bypass, and Patient-Reported Outcomes Measurement Information System Physical Scores Predicted Electroencephalogram Burst-suppression. After backward elimination, only alpha power, lowest temperature during CPB, and Patient-Reported Outcomes Measurement Information System Physical were retained as significant predictors. (These predictors had near zero correlations with each other in our sample; thus, multicollinearity was not of concern.) The overall model of all three was also significant (Likelihood Ratio: 46.4, $P < 0.001$): alpha power (odds ratio, 0.61 [0.47 to 0.76]; $P < 0.001$), lowest temperature during CPB (odds ratio, 0.73 [0.58 to 0.88]; $P = 0.003$), and Patient-Reported Outcomes Measurement Information System Physical (odds ratio, 0.96 [0.91 to 0.99]; $P = 0.044$) were retained as significant predictors (fig. 2). The area under the receiver operating curve for this model was 0.84. Incidentally, the three significant predictors that we found after backward elimination were also individually significant, and no others were, in the initial model before backward elimination. Further, our finding was conserved when we ran a limited backward elimination using only predictors that were significant in univariate analyses (alpha power, $P < 0.0001$; lowest temperature during CPB, $P = 0.003$; Patient-Reported Outcomes Measurement Information System Physical, $P = 0.044$). This suggests that our findings were not chance artifacts resulting from the iterative backward elimination procedure.

Age and Burst-Suppression during Cardiopulmonary Bypass Predicted Postoperative Delirium. After backward elimination, only burst-suppression during CPB and age were retained as relevant predictors. The overall model of both predictors was also significant (Likelihood Ratio: 13.1, $P = 0.002$): age (odds ratio, 1.07 [0.99 to 1.15]; $P = 0.090$), and burst-suppression (odds ratio, 4.1 [1.5 to 13.7]; $P = 0.012$; Supplemental Digital Content, fig. 1,

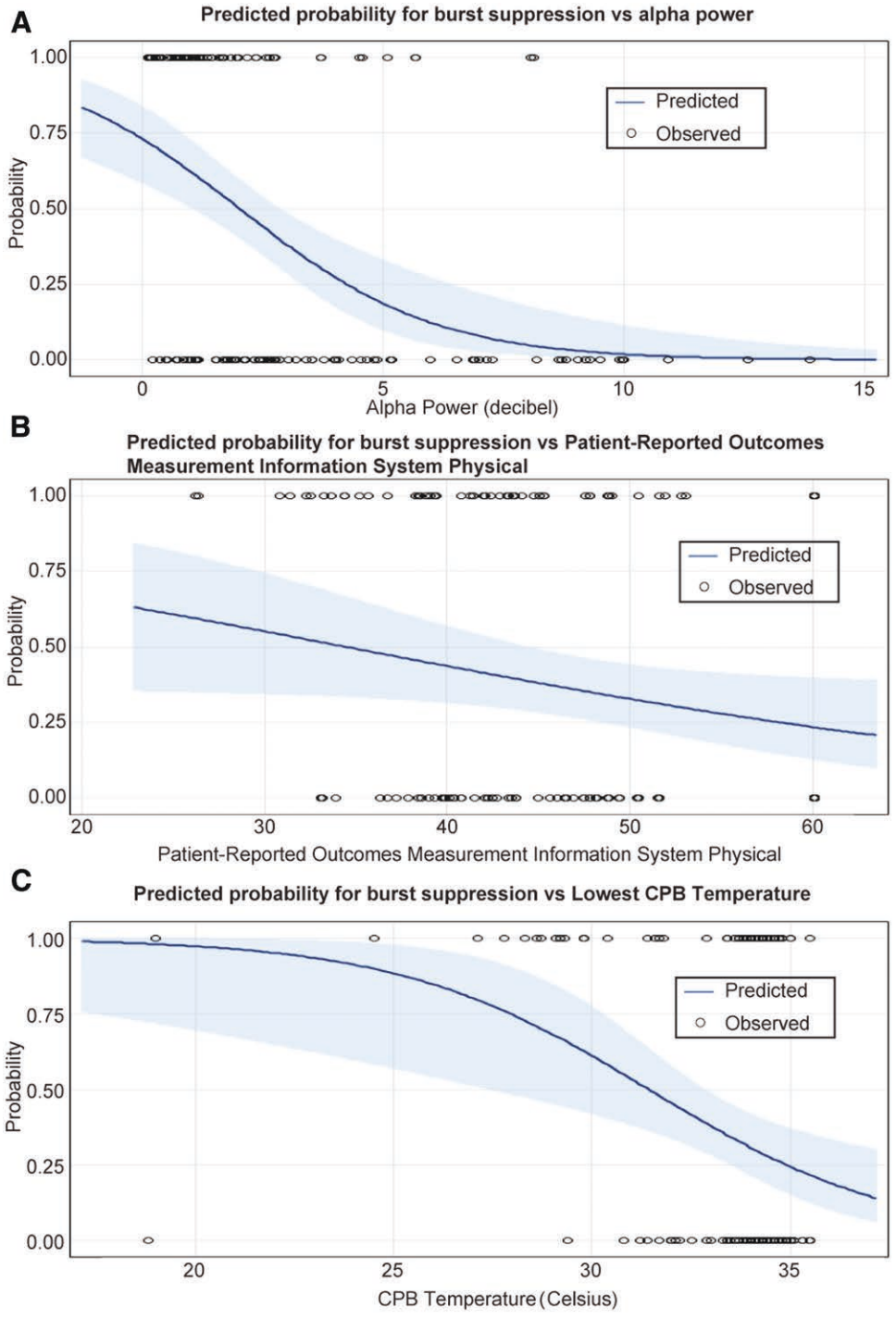

Fig. 2. Predicted probability for burst-suppression during cardiopulmonary bypass (CPB) from multivariable backward logistic regression model. (*A*) Relationship between alpha power and probability of burst-suppression during CPB. Physical function and lowest temperature during CPB were held constant at their grand means of 46.5 and 33.2°C, respectively. (*B*) Relationship between physical function and probability of burst-suppression during CPB. Alpha power and lowest temperature during CPB were held constant at their grand means of 3.1 dB and 33.2°C, respectively. (*C*) Relationship between lowest temperature during CPB and probability of burst-suppression during CPB. Alpha power and physical function were held constant at their grand means of 3.1 dB and 46.5, respectively.

http://links.lww.com/ALN/C389). The area under the receiver operating curve for this model was 0.74. (The point biserial correlation of burst-suppression and age was $r = 0.27$, $P = 0.001$, which was significant given the large sample size but well below the level of concerns associated with multicollinearity). As was the case for the retained predictors of burst-suppression, the significant predictor that we found after backward elimination was also individually significant, and no others were, in the initial model before backward elimination. This indicates that our findings were not chance artifacts resulting from the iterative backward elimination procedure. Further, our finding was conserved when we ran a limited backward elimination using only predictors that were significant in univariate analyses (burst-suppression, $P = 0.0032$).

Based on our two-step multivariable logistic regression approach, our final estimated causal model is illustrated in figure 3.

Electroencephalogram Analyses

Decreased but Distinct Patterns of Broadband Electroencephalogram Power Were Associated with Physical Function, Cognitive Status, and Delirium

Physical Function. We compared electroencephalogram spectral estimates of age-matched patients (n = 34 in each group) with low physical function scores (Patient-Reported Outcomes Measurement Information System Physical ≤ 45; Patient-Reported Outcomes Measurement Information System Global Health Physical ≤ 45, mean age, 71 ± 6.4) with patients with high physical function scores (Patient-Reported Outcomes Measurement Information System Physical > 45; Patient-Reported Outcomes Measurement Information System Global Health Physical > 45; mean age, 70 ± 6.1). The isoflurane concentrations for the electroencephalogram epochs analyzed were 0.8 ± 0.14% and 0.8 ± 0.11% for the low physical function group and high physical function group, respectively ($P = 0.849$). Representative spectrograms and time series data of two age-matched and abbreviated Montreal Cognitive Assessment-matched patients with high and low physical function are shown in Supplemental Digital Content, figure 2 (http://links.lww.com/ALN/C373). We observed decreased power in the low physical function group when compared with high physical function group. This difference met our threshold for statistical significance between 7.3 to 19.0 Hz (fig. 4A).

Delirium. We compared electroencephalogram spectral estimates of age-matched patients (n = 23 in each group) with no delirium (abbreviated Montreal Cognitive Assessment 18 ± 3, Patient-Reported Outcomes Measurement Information System Physical 45 ± 8, mean age 74 ± 6.8) with patients with delirium (abbreviated Montreal Cognitive Assessment 17 ± 3, Patient-Reported Outcomes Measurement Information System Physical 44 ± 9, mean age 74 ± 6.7). The isoflurane concentrations for the electroencephalogram epochs analyzed were 0.8 ± 0.12% and 0.8 ± 0.15% for the no delirium group and delirium group, respectively ($P = 0.249$).

We observed decreased power in the delirium group when compared with no delirium group. This difference met our threshold for statistical significance between 6.84 to 24.41 Hz (fig. 4B).

Cognitive Status. The abbreviated Montreal Cognitive Assessment ranges from 0 to 22 points, and scores are categorized as positive for cognitive impairment if they are at or below 17 (mild cognitive impairment, 13 to 17; mild dementia, 7 to 12; moderate dementia, at or below 6).[23] We computed and compared electroencephalogram spectral

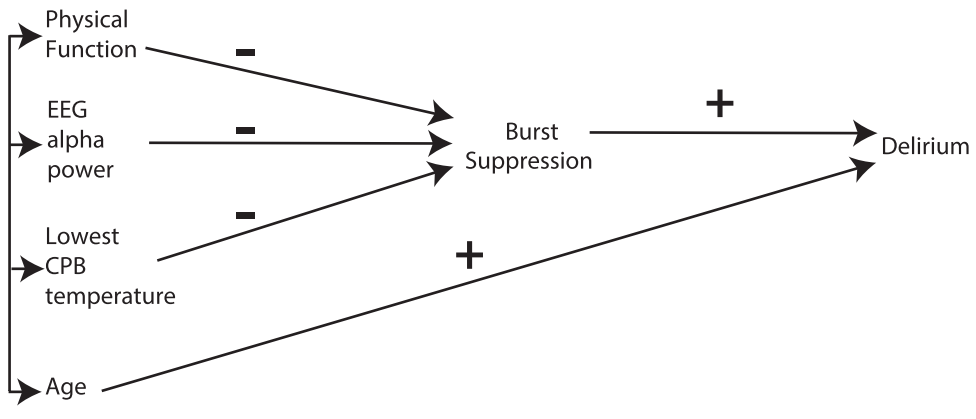

Fig. 3. Final estimated causal model. Physical function, electroencephalogram (EEG) alpha power, and lowest temperature during cardiopulmonary bypass (CPB) have effects on delirium mediated through their impact on burst-suppression during CPB. None of these predictors was found to have a separate direct effect on delirium outside of indirect effects through burst-suppression during CPB. Age had a direct positive effect on delirium. This model also suggests that the significant univariate association of age with burst-suppression during CPB (see Results) may partly be mediated through one or more of the exogenous predictors on the left.

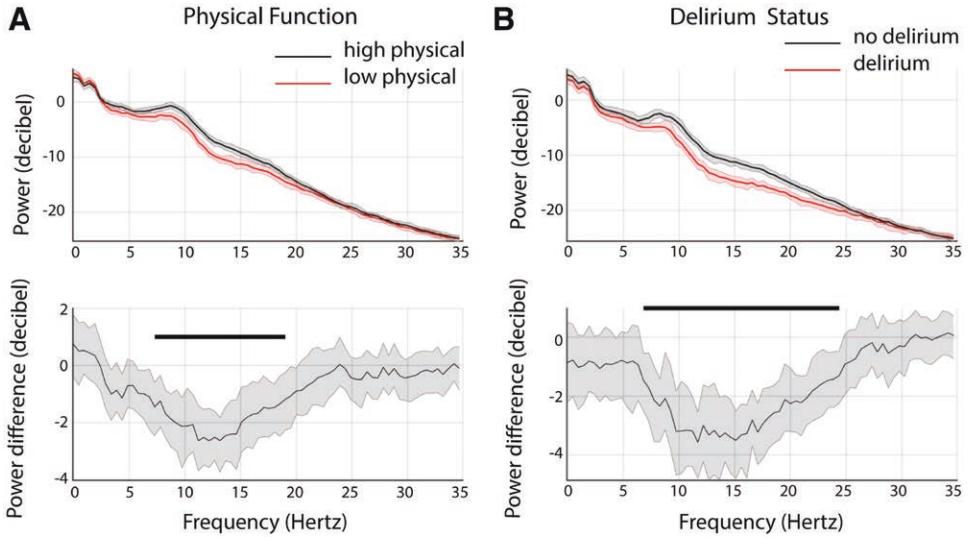

Fig. 4. Group level spectra. (*A*) Power spectra of high physical function (*black*) *versus* low physical function (*red*) groups (*top*). Electroencephalogram power was significantly greater in the high physical function group between 7.3 to 19 Hz (*bottom*, bootstrap difference of mean). (*B*) Power spectra of no delirium (*black*) *versus* delirium (*red*) groups (*top*). Electroencephalogram power was significantly greater in the no delirium group between 6.8 to 24.4 Hz (*bottom*, bootstrap difference of mean). Median bootstrapped spectra presented with 99% CI. *Horizontal solid black lines* represent significantly different frequencies.

estimates of age matched patients (n = 48 in each group) who screened positive for cognitive impairment (abbreviated Montreal Cognitive Assessment at or below 17; mean age, 73 ± 7.3; mean abbreviated Montreal Cognitive Assessment, 15.7 ± 2.5) with age-matched control patients (abbreviated Montreal Cognitive Assessment >18; mean age, 72 ± 6.7; mean abbreviated Montreal Cognitive Assessment, 20.4 ± 3.0). The isoflurane concentrations for the electroencephalogram epochs analyzed were 0.8 ± 0.13% and 0.8 ± 0.13% for the cognitive impairment group and cognitively normal group, respectively ($P = 0.310$). We observed decreased power in the cognitive impairment group (Low abbreviated Montreal Cognitive Assessment) when compared with control patients (High abbreviated Montreal Cognitive Assessment). This difference met our threshold for statistical significance between 4.88 to 9.77 Hz (Supplemental Digital Content, fig. 3, http://links.lww.com/ALN/C374).

Discussion

In this study, we investigated whether burst-suppression during cardiopulmonary bypass mediates the effects of known delirium risk factors on postoperative delirium. Based on a two-step multivariable logistic regression approach, a causal model consistent with the results of our analyses is that burst-suppression during CPB mediates the effects of physical function, lowest temperature during CPB, and alpha power on delirium. Age exhibited a direct effect on delirium in our final estimated model. However, our model also suggests that age may have an indirect effect on burst-suppression during CPB mediated through physical function and alpha power. This is because there was a significant univariate association between age and burst-suppression during CPB. Also, age was significantly correlated with physical function ($r = -0.16$, $P = 0.039$) and electroencephalogram alpha power ($r = -0.33$, $P < 0.001$). Thus, age has an additional indirect effect on delirium through burst-suppression (fig. 3). Taken together, our results suggest that electroencephalogram burst-suppression during cardiopulmonary bypass in elderly patients is a mediator of postoperative delirium.

Intraoperative burst-suppression has been associated with postoperative delirium.[12–14] Our finding that burst-suppression during cardiopulmonary bypass is associated with increased odds of delirium in our univariate analyses and our multivariable model is consistent with these reports.[12–14] However, we note that the probability of postoperative delirium in elderly patients with burst-suppression during cardiopulmonary bypass was less than 0.5 across a range of ages (Supplemental Digital Content, fig. 1, http://links.lww.com/ALN/C389). Thus, the sole use of burst-suppression during cardiopulmonary bypass for the identification of patients at high risk for postoperative delirium may not benefit clinical decision making. Future studies are necessary to make clear whether other electroencephalogram dynamics—from burst-suppression (*e.g.*, burst amplitude) and no burst-suppression epochs (*e.g.*, cross-frequency coupling)—may benefit delirium prediction models.

Although pathophysiologic mechanisms to explain delirium are not clear, there is strong biologic plausibility to suggest that burst-suppression mediates the association between physical function and delirium. Physical activity is associated with increased cerebral blood flow,[24] neurogenesis,[25,26] cell proliferation,[27,28] and synaptic plasticity[29] in laboratory models. In humans, physical activity is associated with increased hippocampal volume,[30,31] improved cognitive function,[32,33] and a decreased incidence of dementia.[30,34,35] These data are consistent with our finding that patients with low physical function scores exhibited a broadband decrease in power between 7.3 to 19 Hz. We note that poor physical function has been associated with delirium after major cardiac surgery.[3] Our finding that patients who subsequently developed postoperative delirium exhibited a broadband decrease in power between 6.8 to 24.4 Hz is consistent with this notion. Thus, decreased broadband electroencephalogram power during isoflurane general anesthesia may reflect deliriogenic structural and perhaps functional brain dynamics.

The underlying mechanism underpinning the decreased broadband power in patients who subsequently screened for delirium is an open question. Anesthetic drugs that significantly modulate γ-aminobutyric acid type A receptors (*i.e.*, isoflurane, sevoflurane) are associated with highly structured oscillations.[36,37] The power of these oscillations exhibits a linear decrease as a function of age to suggest that they arise from intrinsic cellular properties such as synaptic integrity.[38] Holschneider *et al.*[39] demonstrated that a thiopental challenge unmasked an abnormality (decreased beta power during sedation) in frontal electroencephalogram oscillations of patients with Alzheimer's disease that was not discernible at baseline. This abnormality was postulated to result from cortical deafferentation.[39]

Sun *et al.* recently conceptualized *brain age*—different from chronological age—from the electroencephalogram of sleep. They proposed the brain age index (brain age *minus* chronological age) to reflect the degree of deviation from normal aging.[40] Using an interpretable machine learning model based on spectral, entropy, time-series features, patients with neurologic or psychiatric diseases were found to exhibit increased brain age indices compared with healthy controls. Although the concept of brain age has not been applied to intraoperative electroencephalogram data, we conjecture that deviations from chronological aging may have perioperative clinical implications. This is because (1) anesthetic drugs may accentuate differences in electroencephalogram data from pathologic brain regions[39] and (2) we found significant differences in electroencephalogram power of patients with poor physical function and delirium.

Our study has several important limitations. First, we did not measure objective measures of physical function such as gait or grip strength. Second, we studied patients who presented for elective cardiac surgery without clinically diagnosed dementia. Thus, we cannot make inferences on whether cognitive status is associated with intraoperative burst-suppression during CPB in other patient populations (*e.g.*, such as those with a clinical diagnosis of Alzheimer's disease). We note that the abbreviated Montreal Cognitive Assessment is not a substitute for a formal neuropsychologic battery. Third, this study was powered to analyze the association between abbreviated Montreal Cognitive Assessment scores and burst-suppression during CPB. Fourth, anesthetic adjuncts may affect electroencephalogram power. Fifth, we did not analyze spectral characteristics of bursts or the duration burst-suppression. Sixth, our sample size was modest relative to the number of predictors initially considered our multivariable models. Therefore, replication of our findings is recommended in future research. Finally, this was a prespecified substudy of the MINDDS trial where patients were randomized to placebo or dexmedetomidine intervention, an adrenergic sedative medication[41,42] that may affect the incidence of delirium. Thus, the incidence of delirium may have been underestimated in the MINDDS trial cohort.

In conclusion, the present study provides evidence that burst-suppression during CPB in patients older than 60 yr who present for elective cardiac surgery mediates the effect of physical function, alpha power, and lowest temperature during CPB on delirium. We also conclude that patients with postoperative delirium in this cohort possessed a preexisting susceptibility to delirium that was reflected in the intraoperative electroencephalogram as decreased broadband power. A clinical implication of our study is that physical function may be a modifiable risk factor for postoperative delirium. This concept is based on a growing body of evidence that has related cognitive,[43,44] morbidity,[45–48] and mortality[49,50] benefits to physical activity.

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Competing Interests

Dr. Akeju has received speaker's honoraria from Masimo Corporation (Irvine, California) and is listed as an inventor on pending patents on EEG monitoring and sleep that are assigned to Massachusetts General Hospital (Boston, Massachusetts). Dr. Houle is a consultant for GlaxoSmithKline (Brentford, United Kingdom) and is the cofounder of StatReviewer (North Andover, Massachusetts). The other authors declare no competing interests.

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Preoperative Frailty and Postoperative Delirium Independently Predict 180-day Mortality in Older Patients after Orthopedic Trauma Surgery

Running Title: Frailty and POD Independently Predict Mortality

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Conflicts of interests

OA has received speaker's honoraria from Masimo Corporation and is listed as an inventor on pending patents on EEG monitoring that are assigned to Massachusetts General Hospital, some of which are assigned to Masimo Corporation. OA has received institutionally distributed royalties for these licensed patents. All other authors declare that no competing interests exist.

Key points:

Question: Does preoperative frailty explains the association between postoperative delirium and 180-day mortality after orthopedic surgery in older patients?

Findings: In this prospective cohort study, preoperative frailty and postoperative delirium independently predicted 180-day mortality after adjustment for potential confounders.

Meaning: Our findings support screening for preoperative frailty and postoperative delirium in older patients undergoing orthopedic surgery.

Abstract

Background: Frailty is associated with a higher risk for postoperative delirium and mortality. Whether frailty explains the association between postoperative delirium and mortality is unknown. Such a continuum may provide novel insights into prevention strategies for postoperative delirium. We aimed to determine if frailty moderates the relationship between postoperative delirium and mortality. We hypothesized that frailty does not moderate the association between postoperative delirium and postoperative mortality.

Methods: Retrospective cohort study in a single, academic medical center. Participants were patients older than 65 years old who presented an extremity fracture requiring hospitalization without initial intensive care unit admission (n = 558). Patients were recruited between January 2017 through August 2018 and followed daily through their hospitalization up till discharge. Frailty (FRAIL scale) and postoperative delirium (Confusion Assessment Method) were our main exposures and 180-day mortality was the main outcome.

Results: Prevalence of preoperative frailty was 23%. The incidence of postoperative delirium was higher in the frail (20%) and prefrail (11%) compared to non-frail patients (4%). FRAIL scale (OR = 1.72; 95%CI 1.28 – 2.32, p< 0.001) and postoperative delirium (OR = 2.83; 95%CI 1.2 – 6.7, p = 0.018), were associated with postoperative 180-day mortality after adjusting for potential confounders in multiple variable regression analyses. There was no moderation effect between both risk factors.

Conclusions: Frailty and postoperative delirium are independent risk factors for 180-day postoperative mortality in older orthopedic trauma patients. Continued efforts are needed to optimize care to minimize the burden associated with both conditions.
Keywords: frailty, postoperative delirium, mortality, perioperative, older

Glossary of Terms

GIFTS = Geriatric Inpatient Fracture Trauma Service

IRB = Institutional Review Board

LOS = Length of hospitalization

CAM = Confusion Assessment Method

FRAIL scale = fatigue (F), resistance (R), aerobic (A) capacity, illnesses (I) and loss (L) of weight

AUC = area under the receiver operating characteristic curve

ROC = receiver operating characteristic

BMI = body mass index

CCI = Total Charlson Comorbidity Index Score

ASA = American Society of Anesthesiologists Physical Status

OR = Odds Ratio

HR = Hazard Ratio

SD = Standard Deviations

ANOVA = Analysis of variance

MICE = Multiple Imputation with Chain Equations

95%CI = 95% Confidence Interval

Introduction

Postoperative delirium, an acute disorder of attention and cognition, is associated with increased postoperative mortality in older patients. (1) Frailty, characterized by an age-related decline in reserve across multiple physiological systems (2) is also associated with increased postoperative mortality in older patients. (3-8) Postoperative delirium has been suggested as a "marker" of poor cognitive reserve in frail patients. This is because the incidence of postoperative delirium is high in frail patients. (4,9) Also, frailty measures have been suggested to help target patients as a high risk of delirium. (10) These associations have led to the underexplored hypothesis that frailty and delirium exist on a clinical continuum and share pathophysiological mechanisms. (4,11)

Whether frailty explains the association between postoperative delirium and mortality in geriatric patients has important clinical implications. A frailty, postoperative delirium, and postoperative mortality continuum potentially argues for early frailty identification, counseling and shared decision making, and multimodal prehabilitation. (12-14) However, postoperative delirium may independently initiate a cascade of sociological and biological processes that increase the incidence of mortality. An independent association between postoperative delirium and mortality argues for clinical decision support systems to aid diagnosis, hospital-wide prevention and management pathways for frailty and postoperative delirium, independently. (15-20)

To address this knowledge gap, we designed this study to investigate the associations between preoperative frailty, postoperative delirium and postoperative mortality in older patients after orthopedic surgery for traumatic fractures. A board-

certified geriatrician systematically screened for frailty and postoperative delirium in our cohort study. We hypothesized that frailty does not underpin the association between postoperative delirium and postoperative 180-day mortality.

Methods

This study was approved by the Partners Human Research Committee (Boston, Massachusetts, USA) Institutional Review Board (IRB number 2016P002331). Written informed consent was waived by the IRB.

Study design

A retrospective cohort study in a single academic medical center.

Setting

We analyzed prospectively collected data of patients admitted to the Massachusetts General Hospital Geriatric Inpatient Fracture Trauma Service (GIFTS). GIFTS is an inpatient consultation service that is staffed by board-certified geriatricians, who assist the primary admitting services with clinical management. For the present study, all patients who received a GIFTS consultation between January 2017 through August 2018 were eligible for recruitment. All patients were followed daily through their hospitalization up till discharge. Data on mortality were collected on February 1st, 2019. The loss to follow-up date was obtained from our Medical Health Record System on December 26th, 2019. Data analyses were performed after all records were collected.

Participants

Patients are eligible for GIFTS consultation if they: 1) are more than 65 years of age; 2) have an extremity fracture requiring hospitalization; 3) do not have significant

trauma burden other than orthopedic injury; and 4) are not admitted to an intensive care unit upon initial hospitalization.

Outcomes

To understand the contribution of frailty to the effect of postoperative delirium on postoperative mortality, we followed patients postoperatively and registered mortality at 180 postoperative days as our primary outcome. Secondary outcomes included 30-day and 90-day postoperative mortality, survival (difference in days between the date of surgery and loss to follow-up date), length of hospitalization (LOS, the difference in days between the date of hospital admission and date of hospital discharge) and in-hospital mortality (mortality in the period between the date of hospital admission and date of hospital discharge).

Mortality data were obtained from our Medical Health Record System based on healthcare records, obituaries, and Accurint® data. Each patient was followed up for a period between the date of surgery (time 0) and at least six months postoperatively. The loss to follow-up date was defined as the date of death or date of last medical encounter. Follow-up time was calculated from the interval of days between the date of surgery (time 0) to loss to follow-up date.

Exposures

Delirium was assessed daily during hospitalization period by an experienced GIFTS geriatrician using the Confusion Assessment Method (CAM). (21) Postoperative delirium was defined as delirium diagnosed at least once during the postoperative

period between discharge from the post-anesthesia care unit up to the end of the seventh postoperative day or end of hospitalization, whichever came first. Patients with preoperative delirium were excluded from our study cohort.

Frailty was screened by a GIFTS geriatrician at the time of the first preoperative consultation using the FRAIL scale. (22,23) This scale consists of five short questions to assess: fatigue (F), resistance (R), aerobic (A) capacity, illnesses (I) and loss (L) of weight. Each question scores 1 point which sum was used to classify patients into the following categories: robust (score=0), prefrail (score=1–2), and frail (score=3–5). The FRAIL scale was selected for downstream analyses because of previous clinical utility demonstrated in similar populations. (24,25) Also, it offered the best area under the receiver operating characteristic (ROC) curve for 180-day mortality prediction (AUC 80.31%; 95%CI = 73.6 – 87) when compared to other tools.

Multiple frailty assessments measuring functional, nutritional and gait assessments were performed. These data are summarized in Supplemental Table 1.

Covariates

Covariates include age, sex, weight, height, Minicog, Global Deterioration Scale, body mass index (BMI), Total Charlson Comorbidity Index Score (CCI), American Society of Anesthesiologists (ASA) Physical Status score and anesthesia type. Because cognitive data had a high number of missing values, we used the Global Deterioration Scale to impute the missing data in Minicog creating a new combined binary variable: Cognitive deficit. These data are summarized in Supplemental Table 2.

Confounders and bias

Age, sex, CCI, BMI, and Cognitive deficit were considered as potential confounders. Selection bias was managed by including all patients that fulfilled inclusion criteria into the study. Recall bias was minimized because data were collected by geriatricians with the aid of standardized clinical tools. We adjusted our models by known and measured confounders when possible.

Power analysis

There was no a priori power analysis to guide sample size estimation. Utilizing a logistic regression model and two-tailed alpha = 0.05, our observed sample of 558 patients would yield a power of 0.8 to detect the minimal Odds Ratios OR = 1.62 for every 1 standard deviation increase of the total frailty score. This effect size equates to an increase of mortality rates within 180 days from the baseline observed rate of 36/558 = 6.5% to 10.1%, assuming the total frailty score positively correlates with the mortality outcome.

Statistical analysis

Descriptive statistics were summarized by frailty groups (i.e. Robust, Prefrail, and Frail) using means and standard deviations (SD) for numeric variables, and categorical variables were reported using frequencies and percentages. Group comparisons were performed with Pearson's Chi-Squared Test for categorical variables (with continuity correction) and ANOVA for continuous variables. Data missingness characteristics

among study variables were reported using missing rates. Multiple imputations were performed for missing data using the Multiple Imputation with Chain Equations (MICE) method (m = 5).

Survival analysis was conducted using the Cox Regression and Kaplan-Meier curves to compare survival rates for three frail categories (Robust, Prefrail, and Frail). The number of surviving patients, death and censored events were reported using frequencies. Survival analyses were conducted on the unimputed dataset. Proportional hazards assumptions were checked using the Schoenfeld residuals. Univariate logistic regression analyses were conducted to assess for associations between the FRAIL scale (numeric variable, score 1 to 5), postoperative delirium (binary) and 180-day mortality. We assessed whether the combination of frailty and postoperative delirium had a moderation effect on 180-day mortality by comparing model fitness, using likelihood-ratio tests, after including a postoperative delirium-frailty interaction term. For multivariable analyses, we re-performed these analyses with adjustments for age, gender, CCI, Cognitive deficit and BMI. Both the crude Odds Ratios (ORs) from univariate models and adjusted ORs from multivariable models along with their corresponding 95% confidence intervals (95% CI) were reported and compared. Univariate and multivariable logistic regression analyses were performed on MICE-imputed datasets (5 datasets) and estimation results were pooled using Rubin's rules for averaging. (26) Similar regression analyses for 30-day and 90-day mortality were performed. LOS was modelled using linear regression with log transformation.

All analyses were performed using R statistical software V3.6 (Comprehensive R Archive Network, Vienna, Austria). All tests were two-sided, and alpha was set to 0.05.

Patients characteristics associated with frailty

Data from 558 patients were analyzed in this manuscript. Our original cohort (n = 608) included 5 duplicated records and 45 patients with preoperative delirium. A flowchart of patient selection is described in Figure 1.

The prevalence of frailty in our study cohort was 23%. We found that the incidence of postoperative delirium was higher in the prefrail (11%) and the frail (20%) groups, compared to the robust (4%) group. However, most of the measured patient characteristics also differed (Table 1). Missing data for each variable of interest are in Supplemental Table 3.

Primary analysis

Increased 180-day mortality was associated with frailty and postoperative delirium

Survival analyses confirmed increased mortality in the frail group compared to non-frail groups (Cox Regression; Hazard Ratio (HR) = 1.71; 95%CI 1.44 – 2.04, p< 0.001). (Figure 2). We found associations between our exposure measures (FRAIL scale and postoperative delirium) and 180-day mortality in a Cox Proportional Hazard Model that adjusted for potential confounders (age, sex, CCI, Cognitive deficit (yes) and BMI). FRAIL scale (HR = 1.38; 95%CI 1.12 – 1.70, p-value = 0.003), postoperative delirium (HR = 2.02; 95%CI 1.04 – 3.95, p-value = 0.039), and CCI (HR = 1.23; 95%CI

1.09 – 1.38, p-value < 0.001) were retained as significant survival predictors in this model (Supplemental Table 4).

Frail status and postoperative delirium were independently associated with postoperative mortality.

Univariate logistic regression models were created to quantify associations between frailty and postoperative delirium with 180-day mortality. We found that frailty and postoperative delirium were independently associated with 180-day mortality. The odds of 180-day mortality increased by 107% (OR = 2.07; 95%CI 158 – 2.69, p-value < 0.001) for each point increase in FRAIL scale. The odds of 180-day mortality increased by 352% (OR = 4.52; 95%CI 2.13 – 9.58, p-value < 0.001) in patients with postoperative delirium.

Frailty does not moderate the association between postoperative delirium and 180-day mortality.

A multivariable logistic regression model was created to quantify the effect of frailty on the association between postoperative delirium and 180-day mortality. We found that the FRAIL scale and postoperative delirium status were retained as 180-day mortality predictors in the multivariable model. The odds of 180-day mortality increased by 98% (OR = 1.98; 95%CI 1.5 – 2.6, p-value < 0.001) for each point increase in FRAIL scale. The odds of 180-day mortality increased by 205% (OR = 3.05; 95%CI 1.36 – 6.82, p-value = 0.007) in patients with postoperative delirium. We did not find a

moderation effect of frailty on the association between postoperative delirium and 180-day mortality (Likelihood-ratio tests for interaction p = 0.331).

Frailty and postoperative delirium were associated with 180-day mortality after adjusting for confounders.

Multivariable logistic regression models were created to investigate the associations between frailty and postoperative delirium with postoperative mortality (180, 30, and 90 days), adjusted by confounders (age, sex, CCI, Cognitive deficit, BMI). We ran multivariable models including each exposure (FRAIL scale or postoperative delirium) and adjusted for confounders. Then, we studied the adjusted associations of the FRAIL scale and postoperative delirium (including their interaction) with postoperative mortality.

FRAIL scale was associated with 180-day postoperative mortality after adjusting for confounders (Table 2, OR = 1.04; 95%CI 1.02 – 1.05, p-value < 0.001). Postoperative delirium was associated with 180-day postoperative mortality after adjusting for confounders (Table 3, OR = 1.12; 95%CI 1.05 – 1.19, p-value = 0.001). When both exposures were included in a model, FRAIL scale (OR = 1.72; 95%CI 1.28 – 2.32, p-value < 0.001) and postoperative delirium (OR = 2.83; 95%CI 1.2 – 6.7, p-value = 0.018) were both associated with 180-day postoperative mortality (Table 4). We did not find any statistically significant interaction between the FRAIL scale and postoperative delirium in the adjusted model (Likelihood-ratio tests for interaction p > 0.999). CCI was associated with 180-day mortality in these models (Table 2, 3 and 4).

Secondary analysis

Frailty was associated with 30-day and 90-day mortality after adjusting for confounders.

FRAIL scale was associated with 30-day mortality after adjusting for confounders (OR = 1.85; 95%CI 1.14 – 2.99, p-value = 0.013). When both exposures were included in a model, only the FRAIL scale (OR = 1.81; 95%CI 1.11 – 2.94, p-value = 0.017) was associated with 30-day mortality. No significant interaction between the FRAIL scale and postoperative delirium (Likelihood-ratio tests for interaction p > 0.999) was found for 30-day mortality in the adjusted model. These data are summarized in Supplemental Tables 5, 6, and 7.

FRAIL scale (OR = 1.73; 95%CI 1.24 – 2.40, p value = 0.001) and postoperative delirium (OR = 3.63; 95%CI = 1.42 – 9.29, p value = 0.007) were associated with 90-day mortality after adjusting for confounders. When both exposures were included in a model, FRAIL scale (OR = 1.67; 95%CI 1.20 – 2.34, p value = 0.003) and postoperative delirium (OR = 3.15; 95%CI 1.19 – 8.29, p value = 0.021) were both associated with 90-day mortality. No significant interaction between FRAIL scale and postoperative delirium (Likelihood-ratio tests for interaction p > 0.999) was found for 90-day mortality. CCI (OR = 1.33; 95%CI 1.12 – 1.58, p value = 0.002) was also associated with 90-day mortality. These data are summarized in Supplemental Tables 8, 9, and 10.

Frailty and postoperative delirium were associated with increased hospital length of stay.

Multivariable linear regression models were used to assess associations between exposure measures (FRAIL scale and postoperative delirium), and length of hospital stay (LOS).

FRAIL scale was associated with increased LOS (Supplemental Table 11, Estimate = 1.04; 95%CI 1.01 – 1.07, p value = 0.006). Postoperative delirium was also associated with increased LOS (Supplemental Table 12, Estimate = 1.17; 95%CI 1.04 – 1.32, p value = 0.012). When included in a model with both exposures, FRAIL scale (Estimate = 1.04; 95%CI 1.01 – 1.07, p value = 0.013) and postoperative delirium (Estimate = 1.15; 95%CI 1.02 – 1.30, p value = 0.026) were both associated with LOS. We did not find statistically significant interaction between FRAIL scale and postoperative delirium in the adjusted model (Supplemental Table 13, Likelihood-ratio tests for interaction p = 0.982).

Discussion

In this study, we investigated whether frailty explains the association between postoperative delirium and postoperative mortality in orthopedic trauma surgical patients >65 years of age. We found that frailty and postoperative delirium were independently associated with 180-day mortality. We also found that frailty did not moderate the effect of postoperative delirium on 180-day mortality. These findings challenge the assertion that frailty explains the association between postoperative delirium and mortality in older surgical patients. The clinical implication of our findings is that concerted efforts to mitigate the risks associated with both frailty and postoperative delirium are necessary.

Consistent with previous studies, we found previously described associations between frailty and postoperative mortality (90-day and 180-day), (8,27) postoperative delirium and postoperative mortality (90-day and 180-day), (1) and frailty and postoperative delirium. (4,9) We also found previously described associations between frailty and increased hospital LOS, (28) and between postoperative delirium and increased hospital LOS. (29,30) However frailty, but not postoperative delirium, was associated with 30-day mortality. We conjecture that this finding is because the sociological and biological underpinnings of 30-day mortality in patients with frailty are distinct from patients with postoperative delirium.

A prior study proposed that delirium foreshadows frailty in older persons experiencing an acute clinical event. (11) Eeles et al. (4) studied a prospective cohort of geriatric patients acutely admitted to a general medicine service. They found that delirium was associated with increased levels of frailty and that the combination of frailty and delirium resulted in increased mortality. In the present study, we found no

moderation effect of frailty in the relation between postoperative delirium and mortality. It is unknown if the differences between medical versus orthopedic populations explain those findings.

The construct of frailty is complex and there are no standardized approaches to measure it in the preoperative setting. In this study, we assessed frailty using the FRAIL questionnaire. (25) The advantage of this scale is that it is brief and easy to administer. Because there is a marked variation in how frailty is assessed, future studies are necessary to identify key frailty domains or consensus frailty screening instruments that are practical in preoperative clinical use. (25,31-35)

The burden of frailty on postoperative morbidity and mortality may be modifiable. For example, weight gain (lean body mass) and improved physical function are preoperative approaches that have recently been shown to decrease postoperative mortality.(12,14,17,36,37) Preoperative frailty screening using the FRAIL scale enables the identification of frail subjects but also those that are undergoing a transition from a robust to a frail state (prefrail). (24) These subjects, which might be candidates for multimodal prehabilitation programs, could benefit from proper frailty identification in elective trauma settings. (12,36,38)

Our study has several strengths. First, a board-certified geriatrician performed a comprehensive geriatric assessment, including the FRAIL scale. Second, daily follow-up and delirium assessments were also performed by a board-certified geriatrician. Third, care pathways were standardized in our study cohort. Limitations of our study involve the inclusion of only one type of patient population. Whether BMI is the best covariate to represent nutritional status for model adjustment is unknown. Also, retrospective nature

of our data does not preclude bias introduced by unknown or unmeasured confounders. In addition, selection of our adjusting variables was based on our pre-existing clinical knowledge, which might have excluded important covariates and change our results. Moreover, delirium is a time fluctuating diagnosis and may have been missed in some patients. Finally, this study was conducted at a single center. Thus, the generalizability of our findings may be limited to tertiary care centers with populations and geriatric care pathways that are similar to ours.

We conclude that frailty and postoperative delirium are independent risk factors for 180-day mortality in geriatric patients with traumatic orthopedic fractures. Efforts dedicated to mitigating the risks associated with frailty (prehabilitation, discharge services), and postoperative delirium (management pathways) are necessary.

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Legends

Figure 1. Flowchart of cohort selection.

Figure 2. Survival probability of patients with different preoperative frail categories.

Table 1. Patient characteristics stratified by frailty status.

Table 2. Multivariable logistic regression model for the association between the FRAIL scale with 180-day mortality.

Table 3. Multivariable logistic regression model for the association between postoperative delirium with 180-day mortality.

Table 4. Multivariable logistic regression model for the association between the FRAIL scale and postoperative delirium with 180-day mortality.

Supplemental Information

Additional Supplemental Information may be found in the online version of this article:

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Supplemental Table 3: Frequency of missing data in each variable.

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Supplemental Table 7: Multivariable logistic regression model for the association between FRAIL scale and postoperative delirium with 30-day mortality.

Supplemental Table 8: Multivariable logistic regression model for the association between the FRAIL scale with 90-day mortality.

Supplemental Table 9: Multivariable logistic regression model for the association between postoperative delirium with 90-day mortality.

Supplemental Table 10: Multivariable logistic regression model for the association between FRAIL scale and postoperative delirium with 90-day mortality.

Supplemental Table 11: Multivariable logistic regression model for the association between the FRAIL scale and LOS.

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Supplemental Table 13. Multivariable logistic regression model for the association between FRAIL scale and postoperative delirium with LOS.

Tables

Table 1. Patient characteristics stratified by frailty status.

Table 1		robust n = 166	prefrail n = 217	frail n = 126	p-value
Age, mean (SD)		77 (8)	81 (9)	83 (8)	<0.001
Sex, n (%)	male	56 (33.9)	64 (29.5)	29 (23.0)	0.128
	female	109 (66.1)	153 (70.5)	97 (77.0)	
Height, mean (SD)		1.66 (0.11)	1.64 (0.10)	1.62 (0.11)	0.014
Weight, mean (SD)		74 (19)	69 (17)	67 (21)	0.007
BMI, mean (SD)		26.58 (5.90)	25.63 (5.49)	25.16 (6.17)	0.095
CCI, mean (SD)		4.93 (2.16)	6.36 (2.52)	7.40 (2.26)	<0.001
ASA Physical Status, n (%)	1	4 (2.5)	0 (0.0)	0 (0.0)	<0.001
	2	83 (52.2)	44 (20.9)	8 (6.7)	
	3	69 (43.4)	157 (74.4)	98 (82.4)	
	4	3 (1.9)	10 (4.7)	13 (10.9)	
MNA, mean (SD)		13 (1)	12(2)	10 (3)	<0.001
Cognition Deficit n (%)	no	129 (81.1)	138 (69.0)	62 (57.9)	<0.001
	yes	30 (18.9)	62 (31.0)	45 (42.1)	
Katz ADL, mean (SD)		6 (0)	6 (1)	4 (2)	<0.001
Lawton IADL, mean (SD)		7 (2)	5 (3)	2 (3)	<0.001
Ambulation, n (%)	no ambulation	0 (0.0)	5 (2.3)	7 (5.8)	<0.001
	dependent	0 (0.0)	10 (4.7)	14 (11.6)	
	independent	166 (100.0)	200 (93.0)	100 (82.6)	
Ambulation aid, n (%)	no	137 (82.5)	84 (38.7)	19 (15.1)	<0.001
	yes	29 (17.5)	133 (61.3)	107 (84.9)	
Falls, n (%)	none	127 (77.4)	119 (57.2)	48 (41.4)	<0.001
	1 fall	22 (13.4)	56 (26.9)	30 (25.9)	
	2 or more falls	15 (9.1)	33 (15.9)	38 (32.8)	
Anesthesia type, n (%)	general	136 (83.4)	185 (87.7)	106 (84.8)	0.491
	spinal	27 (16.6)	26 (12.3)	19 (15.2)	
Postoperative delirium, n (%)	no	160 (96.4)	193 (88.9)	101 (80.2)	<0.001
	yes	6 (3.6)	24 (11.1)	25 (19.8)	
In-hospital mortality, n (%)	no	165 (100.0)	217 (100.0)	122 (96.8)	0.002
	yes	0 (0.0)	0 (0.0)	4 (3.2)	
LOS, mean (SD)		6 (3)	7 (5)	8 (7)	0.004

BMI (Body Mass Index), CCI (Charlson Comorbidity Index), ASA (American Society of Anesthesiologists), MNA (Mini nutritional assessment), ADL (Activities of daily living), IADL (Instrumental activities of daily living), LOS (Length of stay).

Table 2. Multivariable logistic regression model for the association between FRAIL scale with 180-day mortality.

180-day mortality	OR	CI 95%		P-value
FRAIL scale	1.04	1.02	1.05	<0.001
Age	1.00	1.00	1.00	0.834
Sex (female)	1.01	0.96	1.05	0.741
CCI	1.02	1.01	1.03	<0.001
Cognition Deficit (yes)	0.99	0.94	1.04	0.618
BMI	1.00	0.99	1.00	0.031

BMI (Body Mass Index), CCI (Charlson Comorbidity Index).

Table 3. Multivariable logistic regression model for the association between postoperative delirium with 180-day mortality.

180-day mortality	OR	CI 95%		P-value
Postoperative delirium	1.12	1.05	1.19	0.001
Age	1.00	1.00	1.00	0.897
Sex (female)	1.02	0.98	1.07	0.336
CCI	1.02	1.01	1.03	<0.001
Cognition Deficit (yes)	0.99	0.95	1.04	0.718
BMI	1.00	0.99	1.00	0.016

BMI (Body Mass Index), CCI (Charlson Comorbidity Index).

Table 4. Multivariable logistic regression model for the association between FRAIL scale and postoperative delirium with 180-day mortality.

180-day mortality	OR	CI 95%		P-value
FRAIL scale	1.72	1.28	2.32	<0.001
Postoperative delirium	2.83	1.2	6.7	0.018
Age	1.03	0.97	1.08	0.347
Sex (female)	1.32	0.51	3.43	0.568
CCI	1.35	1.15	1.59	<0.001
Cognition Deficit (yes)	0.81	0.34	1.91	0.627
BMI	0.93	0.86	1.01	0.067
FRAIL scale *Postoperative delirium				>0.999*

*No significant interaction between FRAIL scale and postoperative delirium. BMI (Body Mass Index), CCI (Charlson Comorbidity Index).

Figures

Figure 1.

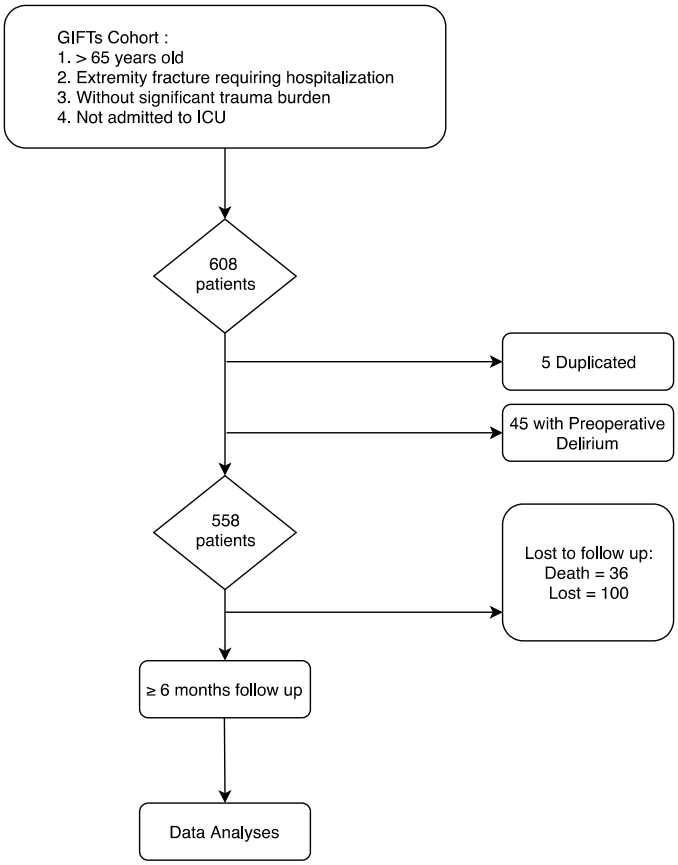
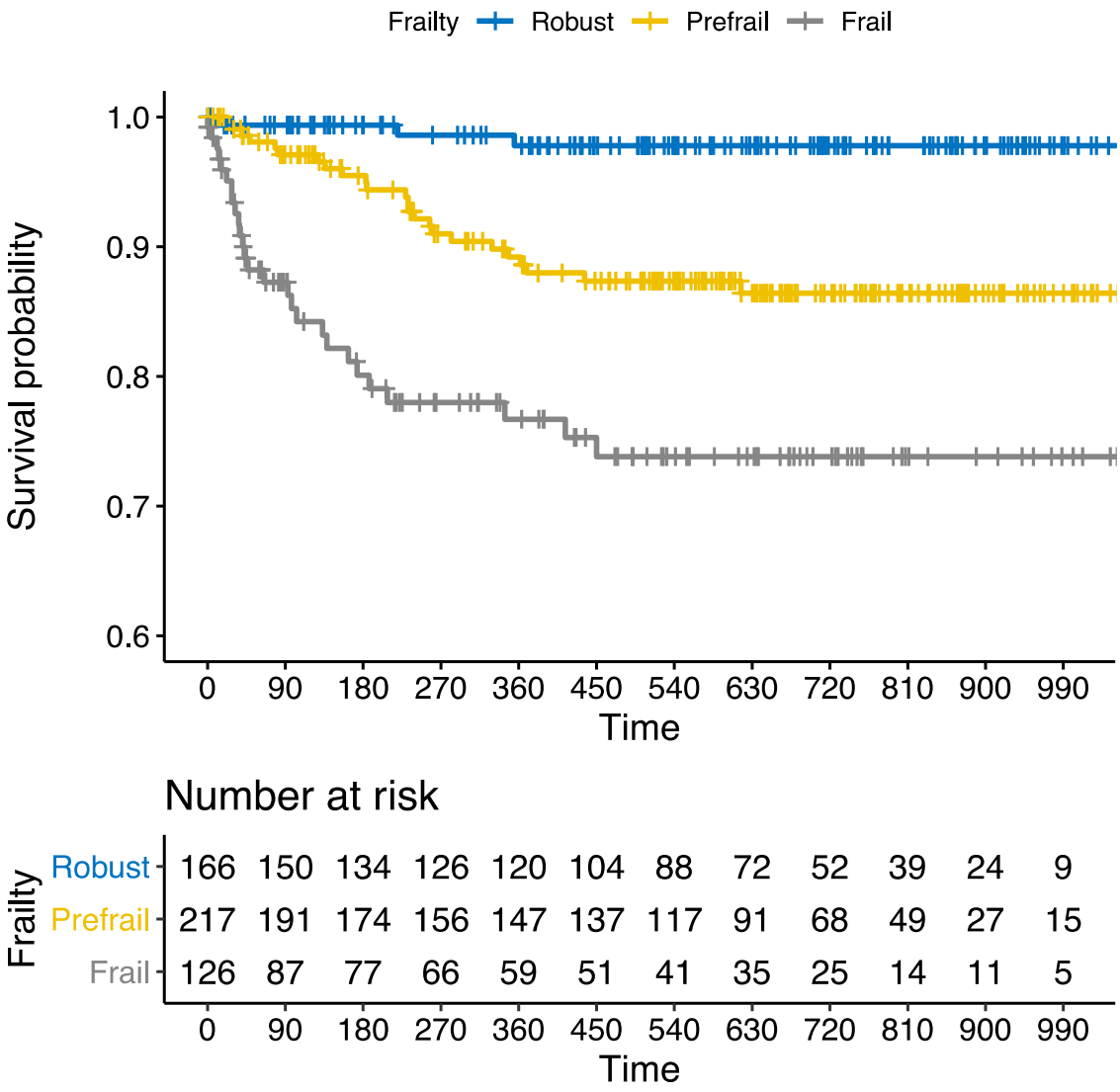


Figure 2.


Frailty
Robust
Prefrail
Frail
Survival probability
1.0
0.9
0.8
0.7
0.6
0
90
180
270
360
450
540
630
720
810
900
990
Time
Number at risk
Frailty
Robust 166 150 134 126 120 104 88 72 52 39 24 9
Prefrail 217 191 174 156 147 137 117 91 68 49 27 15
Frail 126 87 77 66 59 51 41 35 25 14 11 5
0
90
180
270
360
450
540
630
720
810
900
990
Time

Supplemental Table 1. Assessment tools used for frailty screening.

Assessment tool	Description	Interpretation	Reference
Katz Activities of Daily Living (ADL)	Assessment of a subject's functional ability to perform activities of daily living.	0 points (very dependent) 6 points (independent)	Katz S. Assessing self-maintenance: activities of daily living, mobility, and instrumental activities of daily living. J Am Geriatr Soc. 1983;31(12):721-7. (51) (51) (51) (51) (51) (51) (1) (1) (1) (1) (65) (65)
Lawton Instrumental Activities of Daily Living (IADL)	An instrument to assess independent living skills	0 points (very dependent) 8 points (independent)	Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969;9(3):179-86.
Functional Ambulation Classification	Functional walking test that evaluates ambulation ability	0 points (non-functional) 5 points (independent)	Holden MK, Gill KM, Magliozzi MR, Nathan J, Piehl-Baker L. Clinical gait assessment in the neurologically impaired. Reliability and

			meaningfulness. Phys Ther. 1984;64(1):35-40.
Mini Nutritional Assessment	Nutrition screening tool for older patients (> 65 years)	0 to 7 points (malnourished) 8 to 11 points (at risk of malnutrition) 12 to 14 points (normal nutritional status)	1. Guigoz Y, Vellas B. The Mini Nutritional Assessment (MNA) for grading the nutritional state of elderly patients: presentation of the MNA, history, and validation. Nestle Nutr Workshop Ser Clin Perform Programme. 1999;1:3-11; discussion -2. 2. Guigoz Y, Vellas B, Garry PJ. Assessing the nutritional status of the elderly: The Mini Nutritional Assessment as part of the geriatric evaluation. Nutr Rev. 1996;54(1 Pt 2): S59-65. 3. Guigoz Y, Vellas BJ. [Malnutrition in the elderly: the Mini Nutritional

			Assessment (MNA)]. Ther Umsch. 1997;54(6):345-50.
Ambulation aid	In need of ambulation aid?	1 point (Yes) 0 points (No)	
Falls	Number of falls within the last year	0 points (None falls) 1 point (1 fall) 2 points (2 or more falls)	

Supplemental Table 2. Covariates summary table.

Covariate variable	**Unit or classification measure**
Age	Years
Sex	Male or female
Weight	Kilograms
Height	Meters
BMI	Kilograms/meters$_2$
Minicog	Positive or negative
Global Deterioration Scale	1 point (no cognitive decline) to 7 points (severe dementia)
Cognitive Deficit	We collected the positive (1) or negative (0) values of Minicog screening. If there was no value for Minicog in a particular individual, we categorized the Global Deterioration Scale of that subject into a binary variable. If the Global Deterioration Scale presented a value of 1 (no cognitive decline), we assigned a value of 0 to our new cognition variable. If the Global Deterioration Scale presented a value greater than 1, we assigned a value of 1 to our new cognition variable.
Total Charlson Comorbidity Index	1 point to 15 points. Refer to Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.
ASA Physical Status	I = normal healthy patient II = patient with mild systemic disease III = patient with severe systemic disease IV = patient with severe systemic disease that is a constant threat to life V = moribund patient which is not expected to survive without the operation

	VI = brain-dead patient whose organs are being removed for donor purposes
Anesthesia Type	General versus spinal anesthesia

Supplemental Table 3. Frequency of missing data in each variable.

Variable	n	%
Age	1	0.2
Sex	1	0.2
Height	2	0.4
Weight	2	0.4
BMI	2	0.4
CCI	51	9.1
ASA Physical Status	23	4.1
Nutritional Assessment	78	14
Minicog	124	22
Global Deterioration Scale	271	49
Cognition Deficit	66	12
Katz ADL	41	7.3
Lawton IADL	36	6.5
Ambulation	15	2.7
Ambulation aid	0	0
Falls	33	5.9
Anesthesia type	10	1.8
Postoperative delirium	0	0
In-hospital mortality	1	0.2
LOS	0	0

BMI (Body Mass Index), CCI (Charlson Comorbidity Index), ASA (American Society of Anesthesiologists Physical Status), ADL (Activities of Daily Living), IADL (Instrumental Activities of Daily Living), LOS (Length of hospitalization).

Supplemental Table 4. Cox Proportional Hazard Model.

Cox Model Survival	HR	CI 95%		P-value
FRAIL scale	1.38	1.12	1.70	0.003
Postoperative delirium	2.02	1.04	3.95	0.039
Age	1.02	0.98	1.07	0.338
Sex (female)	0.88	0.47	1.68	0.705
CCI	1.23	1.09	1.38	0.001
Cognition Deficit (yes)	0.94	0.49	1.81	0.847
BMI	0.96	0.91	1.02	0.209

BMI (Body Mass Index), CCI (Charlson Comorbidity Index).

Supplemental Table 5. Multivariable logistic regression model for the association between FRAIL scale with 30-day mortality.

30-day mortality	OR	CI 95%		P-value
FRAIL scale	1.85	1.14	2.99	0.013
Age	0.99	0.92	1.07	0.853
Sex (female)	0.65	0.18	2.4	0.523
CCI	1.14	0.9	1.45	0.286
Cognition Deficit (yes)	0.51	0.11	2.33	0.385
BMI	0.99	0.89	1.1	0.83

BMI (Body Mass Index), CCI (Charlson Comorbidity Index)

Supplemental Table 6. Multivariable logistic regression model for the association between postoperative delirium with 30-day mortality.

30-day mortality	OR	CI 95%		P-value
Postoperative delirium	2.35	0.58	9.54	0.233
Age	0.99	0.91	1.07	0.747
Sex (female)	0.84	0.24	2.93	0.783
CCI	1.24	1	1.54	0.053
Cognition Deficit (yes)	0.6	0.13	2.72	0.511
BMI	0.97	0.87	1.08	0.549

BMI (Body Mass Index), CCI (Charlson Comorbidity Index)

Supplemental Table 7. Multivariable logistic regression model for the association between FRAIL scale and postoperative delirium with 30-day mortality.

30-day mortality	OR	CI 95%		P-value
FRAIL scale	1.81	1.11	2.94	0.017
Postoperative delirium	1.81	0.43	7.7	0.419
Age	0.99	0.91	1.07	0.81
Sex (female)	0.67	0.18	2.46	0.544
CCI	1.13	0.89	1.44	0.321
Cognition Deficit (yes)	0.46	0.1	2.17	0.328
BMI	0.99	0.89	1.1	0.796
FRAIL scale *Postoperative delirium				>0.999*

*No significant interaction between FRAIL scale and postoperative delirium. BMI (Body Mass Index), CCI (Charlson Comorbidity Index).

Supplemental Table 8. Multivariable logistic regression model for the association between FRAIL scale with 90-day mortality.

90-day mortality	OR	CI 95%		P-value
FRAIL scale	1.73	1.24	2.40	0.001
Age	1.01	0.95	1.07	0.724
Sex (female)	0.86	0.31	2.35	0.763
CCI	1.34	1.13	1.59	0.001
Cognition Deficit (yes)	0.55	0.19	1.60	0.270
BMI	0.92	0.84	1.01	0.086

BMI (Body Mass Index), CCI (Charlson Comorbidity Index).

Supplemental Table 9. Multivariable logistic regression model for the association between postoperative delirium with 90-day mortality.

90-day mortality	OR	CI 95%		P-value
Postoperative delirium	3.63	1.42	9.29	0.007
Age	1.00	0.94	1.06	0.995
Sex (female)	1.06	0.40	2.80	0.909
CCI	1.42	1.20	1.67	<0.001
Cognition Deficit (yes)	0.62	0.22	1.77	0.371
BMI	0.90	0.82	0.99	0.027

BMI (Body Mass Index), CCI (Charlson Comorbidity Index).

Supplemental Table 10. Multivariable logistic regression model for the association between FRAIL scale and postoperative delirium with 90-day mortality.

90-day mortality	OR	CI 95%		P-value
FRAIL scale	1.67	1.20	2.34	0.003
Postoperative delirium	3.15	1.19	8.29	0.021
Age	1.00	0.95	1.06	0.881
Sex (female)	0.93	0.34	2.58	0.889
CCI	1.33	1.12	1.58	0.002
Cognition Deficit (yes)	0.47	0.16	1.40	0.173
BMI	0.93	0.85	1.01	0.081
FRAIL scale *Postoperative delirium				>0.999*

*No significant interaction between FRAIL scale and postoperative delirium. BMI (Body Mass Index), CCI (Charlson Comorbidity Index).

Supplemental Table 11. Multivariable logistic regression model for the association between FRAIL scale and LOS.

LOS	OR	CI 95%		P-value
FRAIL scale	1.04	1.01	1.07	0.006
Age	1.00	0.99	1.00	0.822
Sex (female)	0.95	0.87	1.03	0.230
CCI	1.02	1.00	1.03	0.074
Cognition Deficit (yes)	1.06	0.96	1.16	0.269
BMI	1.00	0.99	1.01	0.944

BMI (Body Mass Index), CCI (Charlson Comorbidity Index).

Supplemental Table 12. Multivariable logistic regression model for the association between postoperative delirium and LOS.

LOS	OR	CI 95%		P-value
Postoperative delirium	1.17	1.04	1.32	0.012
Age	1.00	0.99	1.00	0.759
Sex (female)	0.97	0.89	1.05	0.427
CCI	1.02	1.00	1.04	0.014
Cognition Deficit (yes)	1.06	0.96	1.16	0.246
BMI	1.00	0.99	1.01	0.916

BMI (Body Mass Index), CCI (Charlson Comorbidity Index).

Supplemental Table 13. Multivariable logistic regression model for the association between FRAIL scale and postoperative delirium with LOS.

LOS	OR	CI 95%		P-value
FRAIL scale	1.04	1.01	1.07	0.013
Postoperative delirium	1.15	1.02	1.30	0.026
Age	1.00	0.99	1.00	0.676
Sex (female)	0.96	0.88	1.04	0.280
CCI	1.02	1.00	1.03	0.098
Cognition Deficit (yes)	1.04	0.95	1.15	0.372
BMI	1.00	0.99	1.01	0.976
FRAIL scale *Postoperative delirium				0.982

*No significant interaction between FRAIL scale and postoperative delirium. BMI (Body Mass Index), CCI (Charlson Comorbidity Index).

Summary

Postoperative delirium is a frequent complication in the surgical older population that imposes economic and health costs. Developing methods to identify patients at risk can help lessen the burden of this syndrome. In our first research, we investigated whether burst-suppression during cardiopulmonary bypass (CPB) mediates the effects of known delirium risk factors on postoperative delirium. The inference from this study is that CPB burst-suppression mediates the effects of physical function, lowest CPB temperature, and electroencephalogram alpha power on delirium. Moreover, patients who present a decreased intraoperative electroencephalogram broadband power possess a pre-existing susceptibility to delirium.

In our second study, we investigated if preoperative frailty had an impact on postoperative delirium reflected on 180-day mortality. Also, we investigated whether preoperative frailty explains the association between postoperative delirium and mortality. We found that frailty and postoperative delirium are independent risk factors for 180-day mortality in geriatric patients with traumatic orthopedic fractures. Efforts dedicated to independently mitigate the risks associated with frailty and postoperative delirium are necessary.

Our research had several important limitations. First, the retrospective nature of our data cannot prevent the existence of residual confounding. Also, the initial selection of our adjusting variables was based on our pre-existing clinical knowledge, which might have excluded important covariates. Our first research, was a pre-specified substudy of the MINDDS trial where patients were randomized to placebo or dexmedetomidine intervention, an adrenergic sedative medication that may affect the incidence of delirium.

Thus, the incidence of delirium may have been underestimated in the MINDDS trial cohort. We did not adjust for randomized arm in delirium model, which might affect our results. We did not measure objective measures of physical function such as gait or grip strength. We did not analyze the spectral characteristics of bursts or the duration of burst-suppression. Also, our sample size was modest relative to the number of predictors initially considered our multivariable models. Therefore, replication of our findings is recommended in future research. In our second research, we included only one type of patient population which can limit generalizability. Also, whether BMI is the best covariate to represent nutritional status for model adjustment is unknown. Moreover, delirium is a time fluctuating diagnosis and may have been missed in some patients. Finally, this study was conducted at a single center. Thus, the generalizability of our findings may be limited to tertiary care centers with populations and geriatric care pathways that are similar to ours.

In conclusion, the present study provides evidence that burst-suppression during CPB in patients older than 60 years who present for elective cardiac surgery mediates the effect of physical function, alpha power, and lowest temperature during CPB on delirium. We also conclude that patients with postoperative delirium in this cohort possessed a preexisting susceptibility to delirium that was reflected in the intraoperative electroencephalogram as decreased broadband power. A clinical implication of our study is that physical function may be a modifiable risk factor for postoperative delirium. In contrast, preoperative frailty is an independent risk factor for postoperative mortality. Methods to efficiently screen for preoperative frailty and postoperative delirium should be implemented in preoperative anesthesia clinics to help decrease their burden.