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Intraoperative electroencephalographic marker of preoperative frailty: A prospective cohort study

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Graphical Abstract

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Author contribution

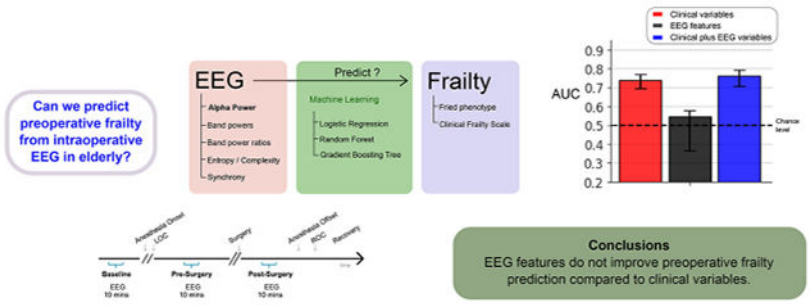
Conceptualization, project administration, and funding acquisition: JCP, MBW, LIC, OA.
Data curation: JCP, MFE, JB, NC, VC, MIM, MC.
Investigation, methodology, and supervision: JCP, GB, HS, LIC, MBW, OA.
Formal analyses: GB, HS.
Writing original draft: GB, HS, JCP, MBW, LIC, OA.
Writing - review and editing: All authors.

Declaration of Competing Interest

Dr. Westover holds stock in Beacon Biosignals, the makers of EEG analysis software. He is not conducting any research sponsored by this company. All other authors state that there have been no involvements that might raise the question of bias in the work reported or in the conclusions, implications, or opinions stated.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinane.2023.111069.



Keywords

Frailty; Fried phenotype; Clinical frailty scale; Electroencephalography; Surgery; Intraoperative

1. Introduction

Frailty is defined as a lack of physiological reserve characterized by an inadequate return to homeostasis after a stressful event [1,2]. In the perioperative setting, frailty has been associated with increased morbidity and mortality [3–6]. Preoperative frailty screening has been recommended in older patients undergoing surgery across different surgical subspecialties [7], and several validated instruments are available for frailty screening [8,9]. However, logistical challenges such as the time required for each evaluation, availability of trained evaluators, and an increasing shift to virtual preoperative visits have made frailty screening difficult to scale as a population health measure and is not systematically assessed [10].

The phenotype [1] (represented by the Fried Phenotype) and the accumulating deficits models [2,11] (assessed with the Clinical Frailty Scale, CFS) have been used to conceptualize frailty [3]. The phenotype presumes that frailty is an internal phenomenon occurring at a cellular level, caused by breakdown and energetic dysregulation that is expressed in a characteristic phenotype. The accumulation deficits model describes frailty as a measurement of the biologic aging process, represented by the number of deficits present across multiple domains.

Intraoperative frontal electroencephalography (EEG) has been used for decades to monitor the anesthetic brain state [12]. Slow and frontal alpha oscillations are prominent and well studies neural oscillations associated with general anesthesia maintained by propofol and anesthetic vapors. Studies have shown that these oscillations change systematically as a function of age [13], drug dose [14], and drug class [15,16]. Recently, decreased frontal alpha band power has been associated with patients with cognitive deficits [17,18], multiple comorbidities [19], and low physical function scores [20]. These findings suggest that the integrity of the neural circuits that generate the frontal alpha oscillations may reflect cellular processes underlying clinically relevant diagnoses, including different frameworks of frailty [3]. However, whether the intraoperative EEG, as well as low intraoperative alpha oscillation power, can enable inferences on the frailty state of patients is unclear.

Here, we aimed to determine an intraoperative frontal EEG marker of preoperative frailty (Fried Phenotype and CFS) in an older population undergoing general anesthesia for elective non-cardiac surgery. We hypothesized that that intraoperative EEG dynamics would sufficiently differentiate frail from non-frail patients.

2. Methods

2.1. Study design, setting and patients

This study is reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. Research protocol was approved by the local ethics committee (Comité de Ética de Ciencias de la Salud Pontificia Universidad Católica de Chile) before data acquisition and registered in ClinicalTrials.gov (NCT04783662).

This was a prospective cohort study conducted at a tertiary medical center (Hospital Clínico Pontificia Universidad Católica de Chile, Santiago, Chile). Written informed consent was obtained during the preoperative visit. Patient recruitment was conducted between May 2021 and March 2022. Data were collected from preoperative assessment, intraoperative electronic health records, and post anesthesia care unit records. Patient follow-up was up to discharge from this unit. Eligibility criteria included patients ≥65 years old scheduled for elective non-cardiac surgery requiring general anesthesia with Sevoflurane with an American Society of Anesthesiologists (ASA) Physical Status I to III. Older patients (≥ 65 years old) scheduled for non-cardiac surgery requiring general anesthesia were recruited from the elective surgeries schedule. Patients were invited to participate during preoperative assessment. Patients with emergency surgery, neurosurgical interventions, histoiy of alcohol abuse, history of recreational psychoactive drug use, or known allergy to anesthetic drugs were excluded.

2.2. Outcome: frailty

Frailty was our primary outcome. It was assessed by a research nurse (N.C.) who was previously trained by two geriatricians (M.I.M., M.C.). Instruction consisted of 3 sessions of 3 h each: personal study of the different scales measured, observation of frailty scales application by geriatricians, and individual assessment of frailty and contrast with measurement by geriatrician. During data collection, any doubt during frailty assessment was discussed with a geriatrician (M.C.). We measured frailty using two scales: the Fried phenotype [1] (1 to 5 points) dichotomized to non-frail ≤2 points and frail ≥3 points; and the CFS [21] (very fit (1 point) to terminally ill (9 points)), dichotomized to non-frail ≤3 points and frail ≥4 points. The dichotomization was done to make sure we have enough patients in the resulting strata.

2.3. Exposure: EEG

2.3.1. EEG recording—EEG was recorded using a SedLine® monitor, with 4 channels at approximated positions Fp1, Fp2, F7, and F8 of the 10–20 international system, at a sampling rate of 178 Hz. We recorded EEG from three 10-min segments (Fig. 1). The first segment comprised a closed-eye resting state prior to anesthesia (Baseline). The second one

started 10 min after anesthesia induction and before surgical incision (Pre-Surgery). The last one was recorded 10 min before anesthesia offset (Post-Surgery).

2.3.2. EEG pre-processing—The author (G.B.) visually inspected all EEG data from each segment and marked artifact-containing periods. Afterwards artifact-free periods were separated into 10-s epochs with 5 s of overlap. All subsequent analyses were done in these 10-s epochs.

EEG feature extraction in Supplementary Methods and Supplementary Table 1.

2.4. Covariates

We collected several clinical and demographic data to be used as covariates, which could be potential confounding factors, including age (years), sex (male or female), BMI (kg/m^2), MiniCog test scores (0 to 5 points, with ≤2 points being possible cognitive impairment), comorbidities and baseline functionality assessed with American Society of Anesthesiologists (ASA) Physical Status (I to III), educational level (elementary school, high school, undergraduate, postgraduate), abbreviated Charlson Comorbidity Index (0 to 10 points), Lee Cardiovascular Index (0 to 6 points), and Barthel Index (0 to 100 points, categorized to 1 independent (100), 2 minimally dependent (≥60), 3 partially dependent (40–55), 4 very dependent (20–35), 5 totally dependent (<20)).

Post-enrollment variables were also recorded but not used in the prediction analysis, including intraoperative and postoperative variables. Intraoperative data included end tidal expiratory Sevoflurane (%) and mean arterial pressure (mmHg). Induction of general anesthesia was protocolized (Fentanyl 3μg/kg, Propofol 1.5 mg/kg, Rocuronium 0.6 mg/kg intravenous bolus) and maintained with Sevoflurane at 1 age adjusted MAC [23] and ± 20% baseline mean arterial pressure (with Phenylephrine infusion). Postoperative data included post anesthesia care unit (PACU) postoperative delirium before discharge, assessed with the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) by a trained resident nurse (positive or negative).

2.5. Machine learning

For each frailty scale (Fried and CFS) and each EEG recording time, we trained three binary machine learning classifiers using covariates only, EEG features only, as well as covariates and EEG features combined. The type of classifiers included logistic regression with ElasticNet (for multivariate feature selection), random forest (RF), and gradient boosting tree (GBT). Each classifier was fitted in three steps. First, to remove irrelevant elements, we excluded features with insignificant univariate Spearman's correlation after correcting for multiple comparisons. Second, the classifier was trained using nested 5-fold cross validation (Supplementary Method) with weights inversely proportional to the number of samples in each class to deal with the imbalance between non-frail and frail patient numbers. Third, probability calibration was done to make sure the estimated probability matches the actual probability in the dataset.

The performance metrics are receiver operator curve (ROC) and area under ROC (AUC) which are common metrics for classification (not robust to class imbalance) and Cohen's

kappa (robust to class imbalance). For AUC, a value of 0.5 indicates random guess. For Cohen's kappa, a value of 0 indicates random guess. Only results from the best performing classifier, GBT, are reported in the main text, while results from logistic regression and RF are reported in Supplementary Table 2.

2.6. Subset analysis

The out-of-sample Cohen's kappa was estimated as a function of age (65 to 90 years old) for the pre-surgery period, and separately for the two frailty outcomes. Since the dataset is relatively small, estimating performance on young or old subsets is problematic due to further reduced sample size. Therefore, we used a weighted approach, i.e., the performance for a given age was obtained from weighted Cohen's kappa, where the weight was defined using a Gaussian kernel with standard deviation following Scott's rule [24]. We reported the results from using covariates only, EEG features only, and covariates and EEG features combined.

2.7. Required sample size estimation

Sample size was estimated by assuming a Spearman correlation between frontal alpha spectral power and Fried phenotype raw scores. To find a correlation of $R = 0.5$, considering a two-sided significance level of 0.01 and a power of 90%, it was necessary to recruit 52 patients. Considering that the EEG is an instrument that is easily affected by noise (interferences, movements, muscular activity), we contemplated a potential 15% sample loss and recruited a total of 60 patients. (R version 4.1.2, "pwr" package version 1.3.0).

2.8. Statistical analysis

For descriptive statistics, continuous data are presented using the mean ± standard deviation or the median and its interquartile range, as appropriate. In addition, groups are compared using Student's *t*-test for independent samples or Mann-Whitney *U* test according to their distribution. In the case of categorical data, they are presented as absolute counts and their corresponding percentage. Differences between groups are studied using Fisher's exact-test or χ^2 test. Correlation is assessed using Spearman's rho and *p*-value since the features do not necessary follow normal distribution. *P*-values were computed based on the two-sided tests at significance level of 0.05. Multiple comparison correction was used for univariate feature selection only, using the Bonferroni method.

Confounding bias was managed by including all known possible confounders variables into the analysis. Selection bias was minimized by including surgeries of different surgical specialties depending on schedule availability. EEG was used for research purpose without selection. Prospectively collected data allowed us to avoid missing data as much as possible. Missing variables were few (Fig. 2), mainly secondary to EEG noise and assumed as missing at random.

Confidence intervals were estimated using bootstrapping, i.e., randomly sample the same number of patients with replacement (with repetition) 1000 times, and then the lower and upper bounds are defined using the 2.5% and 97.5% percentile of the bootstrapped distribution respectively. Data analyses were performed in R (R Foundation for Statistical

Computing, Vienna, Austria https://www.R-project.org) and Python (Python Software Foundation http://www.python.org).

3. Results

3.1. Dataset characteristics

The final cohort had 60 patients. A flowchart of cohort selection is presented on Fig. 2. The patients' ages ranged from 65 to 96 years old. The incidences of different frailty categories, according to binarized Fried Phenotype (non-frail ≤2 points and frail ≥3 points) and CFS (non-frail ≤3 points and frail ≥4 points.) were: no frail 75% and frail 25%; no frail 72% and frail 28%, respectively. Patient characteristics are presented in Table 1. Frail patients were older, presented increased cardiovascular risk factors, and greater dependence when compared to no frail patients. Using the Fried measure, possible cognitive impairment and emergence delirium were higher in frail patients.

3.2. Alpha power did not independendy correlate with preoperative frailty measurements

To evaluate the possible association between relative alpha power and frailty, we studied the correlation between alpha power measured during the pre-surgery period, and frailty assessed with both Frail phenotype and CFS. We found that only alpha power at the pre-surgery period showed a modest but significant negative correlation with CFS (rho = −0.28, $p = 0.03$) but not with Frail phenotype (rho = −0.001, $p = 0.99$). Considering this result, we conducted multiple correlation analyses on alpha power measured on all three periods and both measures of frailty (Supplementary Fig. 2). We found significant correlations between CFS and Frail phenotype (rho = 0.69, $p < 0.001$), and between pre-surgery vs. post-surgery alpha power (rho = 0.69, $p < 0.001$). However, no other significant correlation between frailty and alpha power was found.

Given the relatively small and specific significant correlation found between CFS and pre-surgery alpha power, we wanted to test whether there could be an underlying variable explaining this association. It has been extensively reported that both frailty and alpha power correlate with age, which could explain our result. To test this hypothesis, we conducted a multiple regression analysis using CFS as the dependent variable and both age and pre-surgical alpha power as predictors. We found that when age was included as a covariable, pre-surgical alpha power failed to significantly contribute to explaining CFS values (alpha coefficient $t = -1.41$, $p = 0.17$; Age coefficient $t = 3.1$, $p = 0.003$). Thus, alpha power does not explain frailty values above its known correlation with age.

3.3. EEG features did not improve frailly prediction compared to clinical covanates using machine learning

EEG features were not superior to clinical covariates for frailty classification measured using either Fried Phenotype (Fig. 3) or CFS (Fig. 4) when compared to covariates only, at all three EEG recording periods. The AUC and Cohen's kappa are shown in Table 2.

3.4. Frailty classification performance is age-dependent

The frailty classification performance showed strong age dependence. When classifying Fried phenotype at the pre-surgery period using covariates and EEG features (Supplementary Fig. 3A, blue curve), the maximum Cohen's kappa occurred around 79 years old at 0.61 (0.48–0.71). Including EEG led to small and insignificant improvement (comparing blue to red curve). When classifying CFS at the pre-surgery period using covariates and EEG features (Supplementary Fig. 3B, blue curve), the age-dependence instead shows an increasing Cohen's kappa at older age, indicating difference in Fried phenotype and CFS. Note that the validity of the result is dependent on the age distribution (Supplementary Fig. 3C).

4. Discussion

In this work we assessed the relation between alpha power, and many other EEG features, with the presence and magnitude of frailty in an elder cohort. We found that alpha power was not able to predict frailty above its known relation with age. In the same line, several EEG features did not improve the ability of machine learning models to predict frailty above the use of more conventional clinical variables.

Multiple guidelines recommend frailty assessment in older people presenting for elective surgery [25,26]. However, preoperative frailty is not routinely performed. A recent survey described that the adherence of US anesthesiologists to preoperative frailty evaluation in adults aged 65 and older was 10% or less [10]. Moreover, sometimes it is not possible to measure preoperative frailty. Emergency surgery or patients that are unable to communicate are examples where frailty measurement is not feasible. In consequence, we hypothesized that the intraoperative EEG could be a low-cost, highly available, and objective tool to assess frailty. In this investigation, we examined for associations between frontal alpha EEG power and frailty assessed using Fried and CFS measures. Frail patients were older, presented with cardiovascular risk factors, were more functionally dependent, presented possible cognitive impairment, and increased emergence delirium. Additionally, we found that in older patients undergoing non-cardiac surgery under general anesthesia with Sevoflurane, alpha power did not explain frailty above its known correlation with age. Machine learning classifiers that used other EEG features in addition to alpha power, also did not improve classification of frailty patients compared to using covariates only.

Our findings challenge theories that are currently applied to the construct of frailty [3] and the recent concept of brain frailty or vulnerable brain [27,28]. For example, EEG markers such as low frontal alpha power and burst suppression have been associated with lower baseline cognitive function [17,18] and postoperative delirium [29–31]. Moreover, frailty is associated with postoperative delirium [32–34]. Thus, we expected a correlation specifically between low alpha power and frailty. However, we did not find such association. In contrast, our results point out that frailty is different from brain frailty or vulnerability. One hypothesis that could explain these differences is that frailty assessment tools used in this work represent a physical health measure rather than a brain wellbeing evaluation – a possible brain-body dissociation. Canales et al. [35] have successfully used preoperative point-of-care ultrasound to discriminate between frail and no frail patients, according to

Fried phenotype. This approach focuses on the identification of sarcopenia, a key component of frailty syndrome, that represents frailty as a physical measure. In contrast, previous work has found EEG markers that could potentially identify underlying neurodegenerative disease and dementia progression [36], supporting the idea of using the EEG as a brain health assessment tool. Clarifying and differentiating these two concepts is relevant. Brain frailty or vulnerability may have different markers and preventive approaches than frailty. Future studies should explore further into these discrepancies.

There are several limitations in our study. Our study cohort was an elective heterogenous non-cardiac local surgical population. Whether our results apply to cardiac, or emergency surgical population is unknown. Moreover, there was no external validation to our findings. Our sample size was small. However, some of our results were consistent with previous publications including the associations of frailty with increased age, functional dependence, possible cognitive impairment, and emergence delirium. Also, we only used frontal EEG for our analyses. Nevertheless, anesthetic induced oscillations are prominent in frontal regions and currently clinically available processed EEG monitors only include frontal montages. Furthermore, our initial approach was only to study the associations between frailty and alpha oscillations, while there are existing evidence that slow and theta oscillations are also prominent during general Sevoflurane anesthesia. However, we included these oscillations in following machine learning analyses. EEG quality is also a limitation. As commonly observed in this type of studies, EEG noise was the main cause of missing EEG data. Nevertheless, we believe its occurrence was at random and not a consequence of a systematic matter. Sedline® EEG might not be sufficiently robust to investigate brain health variations occurring in frail subjects. Also, changes in brain health in frail patients, for example in neurophysiological integrity of cortical or subcortical circuits, could be more subtle than what our sample size allowed us to expose. Future studies should address these issues.

In summary, in this prospective cohort study of older elective non-cardiac surgical population, different alpha spectral power and multiple EEG features did not improve frailty prediction when compared to preoperative demographical features. Future larger studies with high density electrodes are needed to confirm our results.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclosure

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Data availability

The data is available upon reasonable request to the corresponding author.

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HIGHLIGHTS

- Frailty was common in elderly patients undergoing non cardiac surgeiy.
- Electroencephalogram alpha-band power does not predict preoperative frailty above patients' age.
- Frailty predictions by machine learning algorithms, were not improved by the addition of electroencephalogram features.
- Frailty might be different to the concept of brain vulnerability, accounting for a possible brain-body dissociation.

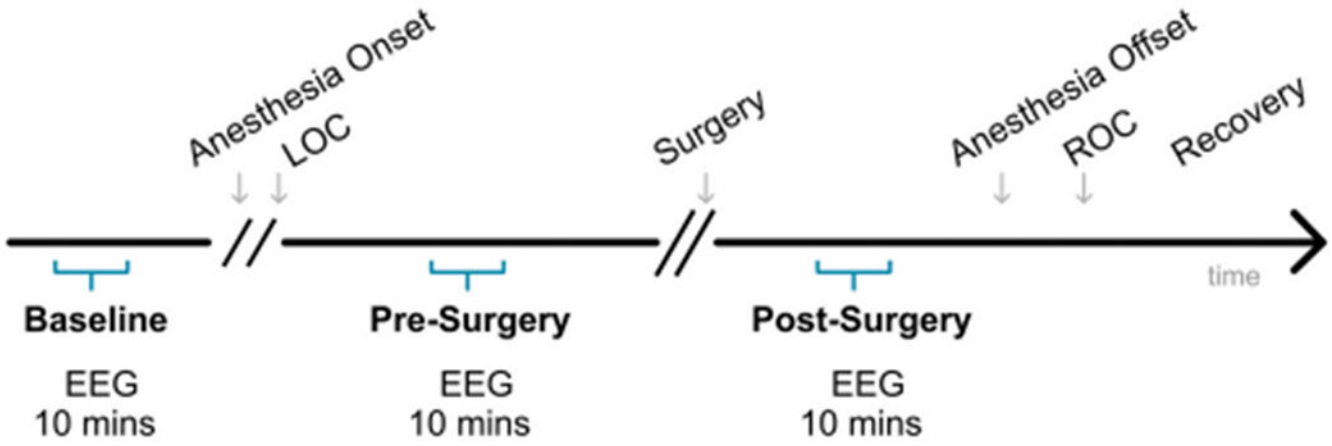

Fig. 1.

Time periods of EEG Data analysis. Depiction of the surgical timeline with emphasis in the three periods in which collected EEG data were obtained. The first period was a closed-eye resting state baseline period during wakefulness. The second one was a pre-surgery period that was obtained 10 min after induction and intubation but mostly before the start of surgery. The third analyzed period, post-surgery period, was obtained 10 min before anesthesia ceased (turn-off volatile agent).

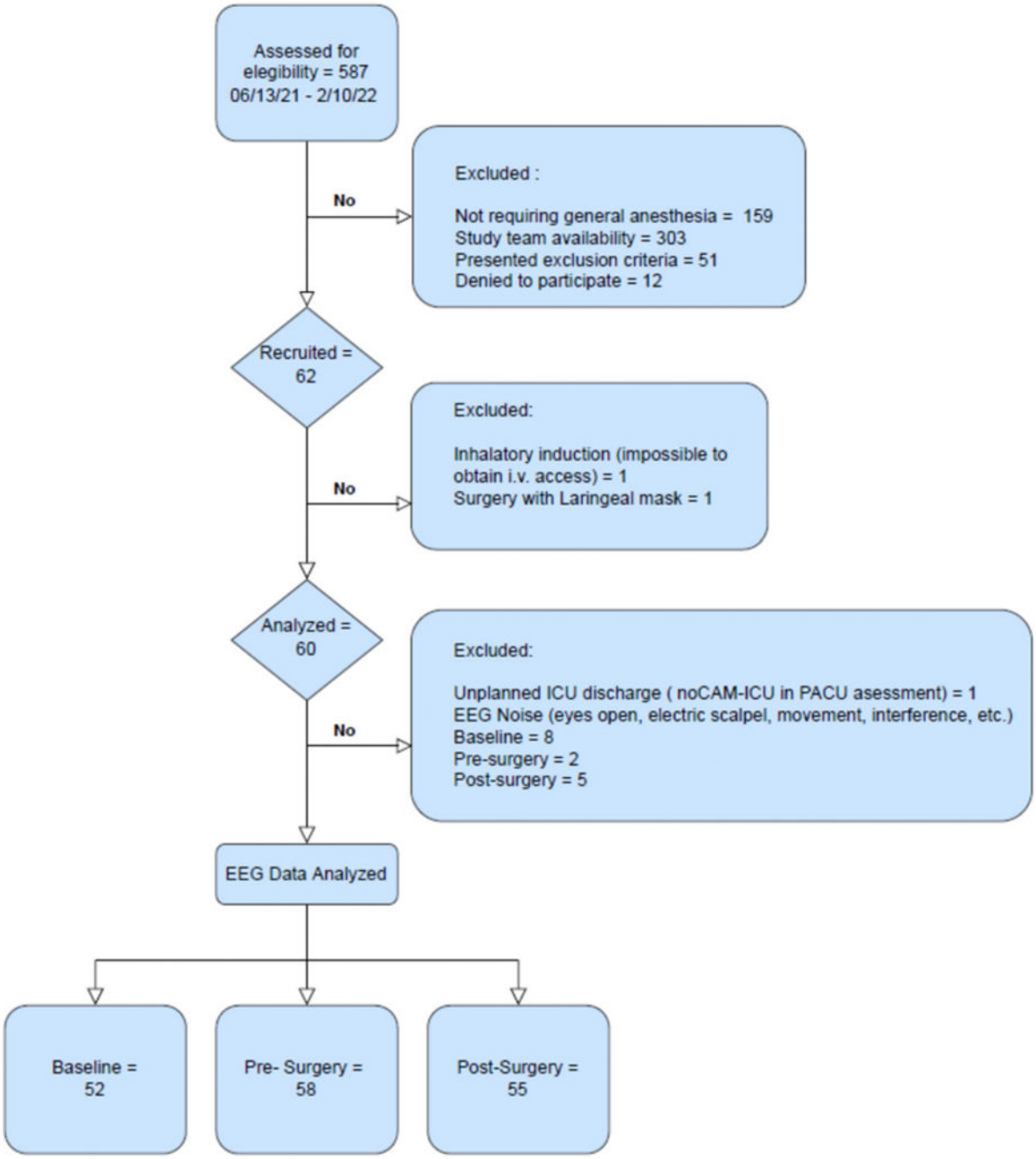

Fig. 2.

Cohort flowchart. A total of 587 patients were screened from the elective non-cardiac surgical schedule at our institution. We recruited 62 patients that gave written informed consent to participate. 60 of them completed perioperative assessments. Adequate EEG data collection was achieved in 52 cases in baseline, 58 cases pre-surgery, and 55 cases post-surgery. One patient did not receive CAM-ICU evaluation in PACU because he was derived to the ICU.

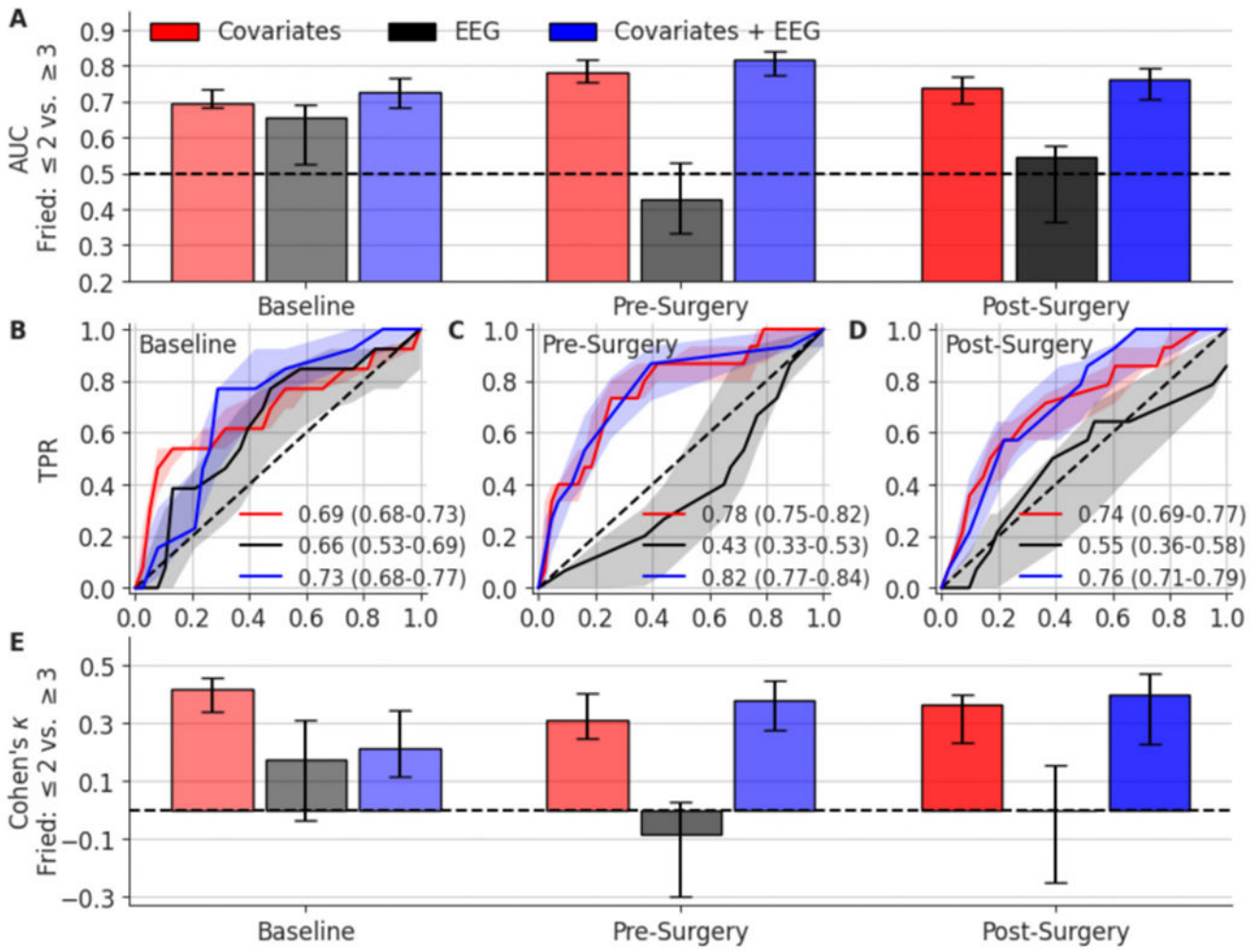

Fig. 3.

GBT classification performances for Fried phenotype (non-frail ≤ 2 points vs. frail ≥ 3 points). (A) The out-of-sample AUC for Fried phenotype, using covariates (red), EEG (black), and covariates and EEG combined (blue), at different EEG recording times. The error bar represents 95% confidence interval from bootstrapping. The dashed horizontal line indicates chance AUC value at 0.5. (B,C,D) The ROCs for every condition. The x-axis is the false positive rate (FPR). The y-axis is the true positive rate (TPR). The curve represents FPR and TPR as a function of threshold applied to the probabilistic output. The shaded area represents the 95% confidence interval. The diagonal dashed red line represents chance level ROC. The AUCs are shown in the legend which are consistent with the numbers in panel A. I The out-of-sample Cohen's kappa for Fried phenotype, using covariates (red), EEG (black), and covariates and EEG combined (blue), at different EEG recording times. The error bar represents 95% confidence interval from bootstrapping. The dashed horizontal line indicates chance Cohen's kappa value at 0. Different than AUC, Cohen's kappa adjusts for imbalanced non-frail vs. frail ratio in the dataset. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

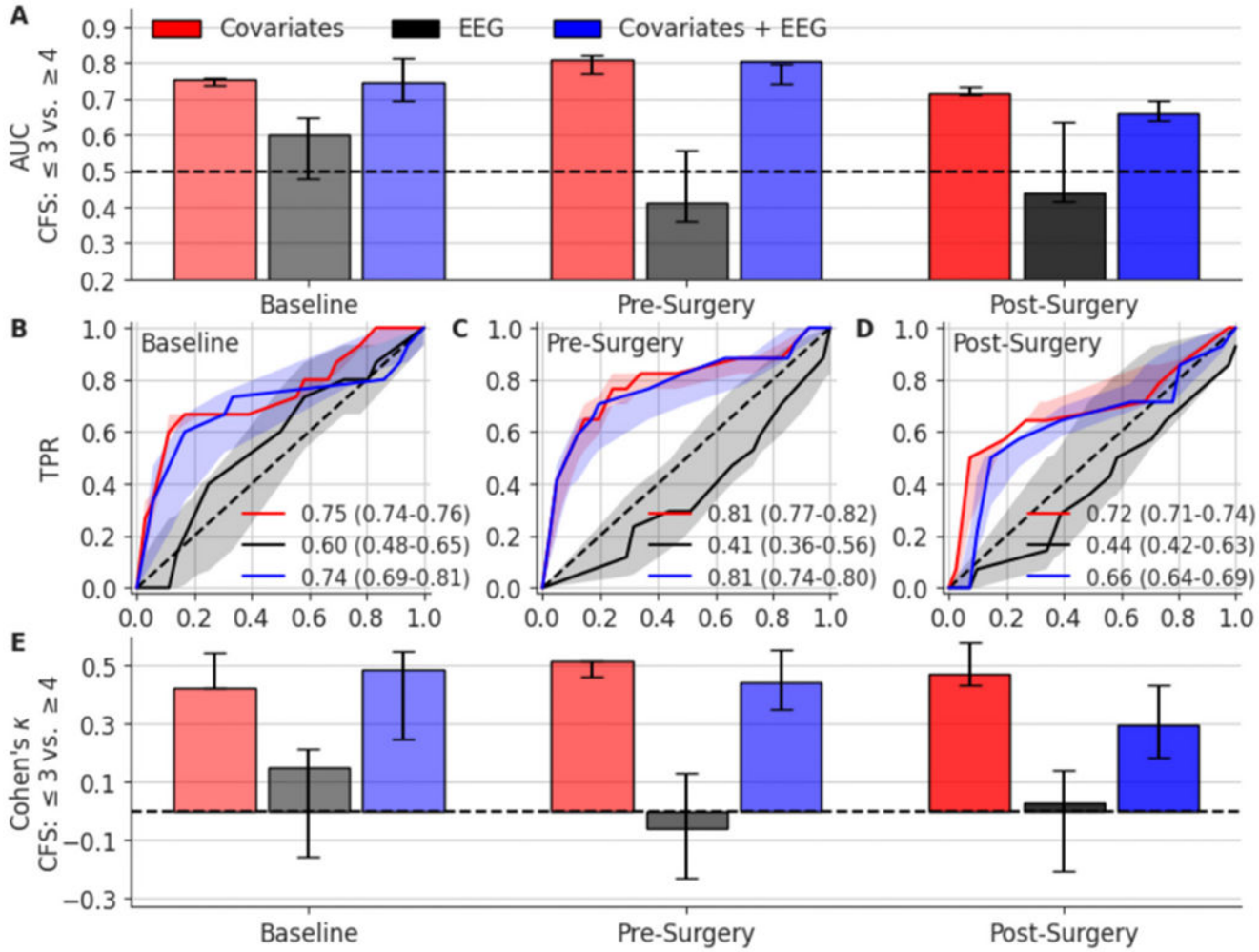

Fig. 4.

GBT classification performances for CFS (non-frail ≤ 3 points vs. frail ≥ 4 points). Organized similarly as in Fig. 3, but for CFS.

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Table 1

Patients' characteristics stratified by Fried phenotype and CFS.

		Stratified by Fried phenotype			Stratified by CFS		
		No Frail	**Frail**	**p**	**No Frail**	**Frail**	**p**
n		45	15		43	17	
Sex (%)	Female	18 (40.0)	5 (33.3)	0.878	17 (39.5)	6 (35.3)	0.992
	Male	27 (60.0)	10 (66.7)		26 (60.5)	11 (64.7)	
Age (median [IQR])		73.00 [70.00, 77.00]	81.00 [76.00, 83.50]	0.005	73.00 [70.00, 77.00]	81.00 [76.00, 84.00]	0.001
Weight (mean (SD))		75.02 (12.19)	72.00 (19.79)	0.484	75.63 (11.66)	70.82 (19.58)	0.245
Height (mean (SD))		164.02 (8.45)	164.00 (11.90)	0.994	164.37 (8.34)	163.12 (11.67)	0.642
BMI (mean (SD))		27.27 (3.71)	26.07 (5.36)	0.338	27.40 (3.61)	25.88 (5.30)	0.208
ASA Physical Status (%)	1	1 (2.2)	0 (0.0)	0.443	1 (2.3)	0 (0.0)	0.17
	2	40 (88.9)	12 (80.0)		39 (90.7)	13 (76.5)	
	3	4 (8.9)	3 (20.0)		3 (7.0)	4 (23.5)	
Educational level (%)	Elementary School	12 (26.7)	7 (46.7)	0.224	11 (25.6)	8 (47.1)	0.109
	High School	11 (24.4)	5 (33.3)		10 (23.3)	6 (35.3)	
	Undergraduate	18 (40.0)	3 (20.0)		18 (41.9)	3 (17.6)	
	Postgraduate	4 (8.9)	0 (0.0)		4 (9.3)	0 (0.0)	
Charlson comorbidity index (%)	0	25 (55.6)	5 (33.3)	0.075	24 (55.8)	6 (35.3)	0.108
	1	11 (24.4)	5 (33.3)		12 (27.9)	4 (23.5)	
	2	8 (17.8)	2 (13.3)		6 (14.0)	4 (23.5)	
	3	1 (2.2)	3 (20.0)		1 (2.3)	3 (17.6)	
Lee cardiovascular index(%)	0	38 (84.4)	8 (53.3)	0.01	37 (86.0)	9 (52.9)	0.004
	1	5 (11.1)	7 (46.7)		4 (9.3)	8 (47.1)	
	2	2 (4.4)	0 (0.0)		2 (4.7)	0 (0.0)	
Barthel (%)	1	45 (100.0)	10 (66.7)	<0.001	42 (97.7)	13 (76.5)	0.031
	2	0 (0.0)	5 (33.3)		1 (2.3)	4 (23.5)	
CFS (%)	Very fit	2 (4.4)	0 (0.0)	<0.001	2 (4.7)	0 (0.0)	<0.001
	Well	24 (53.3)	0 (0.0)		24 (55.8)	0 (0.0)	
	Managing well	15 (33.3)	2 (13.3)		17 (39.5)	0 (0.0)	
	Vulnerable	4 (8.9)	9 (60.0)		0 (0.0)	13 (76.5)	

		Stratified by Fried phenotype			Stratified by CFS		
		No Frail	**Frail**	**p**	**No Frail**	**Frail**	**p**
	Mildly frail	0 (0.0)	4 (26.7)		0 (0.0)	4 (23.5)	
Fried phenotype (%)	Robust	17 (37.8)	0 (0.0)	<0.001	17 (39.5)	0 (0.0)	<0.001
	Prefrail	28 (62.2)	0 (0.0)		24 (55.8)	4 (23.5)	
	Frail	0 (0.0)	15 (100.0)		2 (4.7)	13 (76.5)	
Minicog (%)	Possible cognitive impairment	2 (4.4)	4 (26.7)	0.047	2 (4.7)	4 (23.5)	0.086
	Without cognitive impairment	43 (95.6)	11 (73.3)		41 (95.3)	13 (76.5)	
Emergence Delirium (%)	Positive	0 (0.0)	2 (13.3)	0.039	0 (0.0)	2 (11.8)	0.062
	Negative	44 (97.8)	13 (86.7)		42 (97.7)	15 (88.2)	
	Missing	1 (2.2)	0 (0.0)		1 (2.3)	0 (0.0)	

IQR, interquartile range; SD, standard deviation; BMI, body mass index; ASA, American Society of Anesthesiologists; CFS, Clinical Frailty Scale; CAM-ICU, Confusion Assessment Method for Intensive Care Unit. No frail and frail groups were compared using Student's t-test for independent samples, Mann-Whitney U test, Fisher's exact test or χ^2 test. P-values <0.05 were considered significant.

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Table 2

Frailty classification performance using EEG at different periods using gradient boosting tree (GBT). "[]" indicates 95% confidence interval from bootstrapping 1000 times.

Period	Method + Features	AUC*	Cohen's kappa+
Fried Classification			
pre-surgery	GBT + Covariates only	0.78 [0.75–0.82]	0.31 [0.25–0.40]
	GBT + EEG features only	0.43 [0.33–0.53]	−0.08 [−0.30–0.03]
	GBT + Covariates and EEG features	0.82 [0.77–0.84]	0.38 [0.28–0.45]
baseline	GBT + Covariates only	0.69 [0.68–0.73]	0.42 [0.34–0.46]
	GBT + EEG features only	0.66 [0.53–0.69]	0.17 [−0.03–0.31]
	GBT + Covariates and EEG features	0.73 [0.68–0.77]	0.21 [0.12–0.35]
post-surgery	GBT + Covariates only	0.74 [0.69–0.77]	0.36 [0.23–0.40]
	GBT + EEG features only	0.55 [0.36–0.58]	0.00 [−0.25–0.15]
	GBT + Covariates and EEG features	0.76 [0.71–0.79]	0.40 [0.23–0.47]
CFS Classification			
pre-surgery	GBT + Covariates only	0.81 [0.77–0.82]	0.52 [0.46–0.52]
	GBT + EEG features only	0.41 [0.36–0.56]	−0.06 [−0.23–0.13]
	GBT + Covariates and EEG features	0.81 [0.74–0.80]	0.44 [0.35–0.55]
baseline	GBT + Covariates only	0.75 [0.74–0.76]	0.42 [0.42–0.55]
	GBT + EEG features only	0.60 [0.48–0.65]	0.15 [−0.16–0.21]
	GBT + Covariates and EEG features	0.74 [0.69–0.81]	0.49 [0.25–0.55]
post-surgery	GBT + Covariates only	0.72 [0.71–0.74]	0.47 [0.43–0.58]
	GBT + EEG features only	0.44 [0.42–0.63]	0.03 [−0.20–0.14]
	GBT + Covariates and EEG features	0.66 [0.64–0.69]	0.29 [0.19–0.43]

*AUC ranges from 0 to 1, where 0.5 is random guess, 1 is perfect agreement, and 0 is perfectly opposite.

+Cohen's kappa ranges from −1 to 1, where 0 is random guess, 1 is perfect agreement, and 0 is perfectly opposite. Cohen's kappa considers data imbalance. Cohen's kappa is usually used for inter-rater agreement, but can also be used to evaluate human-model agreement assuming model is another rater.