Game-changing approach for delirium
Novel EEG algorithm for detection and outcome prediction

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Regular Article

Delirium detection by a novel bispectral electroencephalography device in general hospital

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Bispectral EEG (BSEEG) to assess arousal after electro-convulsive therapy (ECT)

Kasra Zarei[a], Nicholas A Sparr[a], Nicholas T Trapp[a], Elena D Neuhaus[a], John W Cromwell[b], Aaron D Boes[a], Gen Shinozaki[a,*]

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Identification of Patients With High Mortality Risk and Prediction of Outcomes in Delirium by Bispectral EEG

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BJPsych The British Journal of Psychiatry (2022) 220, 322–329. doi: 10.1192/bjp.2021.101

Evaluation of point-of-care thumb-size bispectral electroencephalography device to quantify delirium severity and predict mortality

Takehiko Yamanashi, Kaitlyn J. Crutchley, Nadia E. Wahba, Eleanor J. Sullivan, Katie R. Comp, Mari Kajitani, Tammy Tran, Manisha V. Modukuri, Pedro S. Marra, Felipe M. Herrmann, Gloria Chang, Zoe-Ella M. Anderson, Masaaki Iwata, Ken Kobayashi, Koichi Kaneko, Yuhei Umeda, Yoshimasa Kadooka, Sangil Lee, Eri Shinozaki, Matthew D. Karam, Nicolas O. Noiseux and Gen Shinozaki

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Topological data analysis (TDA) enhances bispectral EEG (BSEEG) algorithm for detection of delirium

Takehiko Yamanashi[1,2], Mari Kajitani[3], Masaaki Iwata[2], Kaitlyn J. Crutchley[1], Pedro Marra[1], Johnny R. Malicoat[1], Jessica C. Williams[1], Lydia R. Leyden[1], Hailey Long[1], Duachee Lo[1], Cassidy J. Schacher[1], Kazuaki Hiraoka[3], Tomoyuki Tsunoda[3], Ken Kobayashi[3], Yoshiaki Ikai[3], Koichi Kaneko[2], Yuhei Umeda[3], Yoshimasa Kadooka[4] & Gen Shinozaki[1,5,6,7,8]✉

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ELSEVIER

Regular Research Article

Bispectral EEG (BSEEG) Algorithm Captures High Mortality Risk Among 1,077 Patients: Its Relationship to Delirium Motor Subtype

Yoshitaka Nishizawa, M.D., Ph.D., Takehiko Yamanashi, M.D., Ph.D., Taku Saito, M.D., Ph.D., Pedro Marra, Kaitlyn J. Crutchley, Nadia E. Wahba, M.D., Johnny Malicoat, Kazuki Shibata, Ph.D., Tsuyoshi Nishiguchi, M.D., Ph.D., Sangil Lee, M.D., Hyunkeun R. Cho, Ph.D., Tetsufumi Kanazawa, M.D., Ph.D., Gen Shinozaki, M.D.

Question

Why do we measure blood pressure?

How about glucose?

Your grandma in a hospital

Delirium and mortality (Arch Int Med 2002)

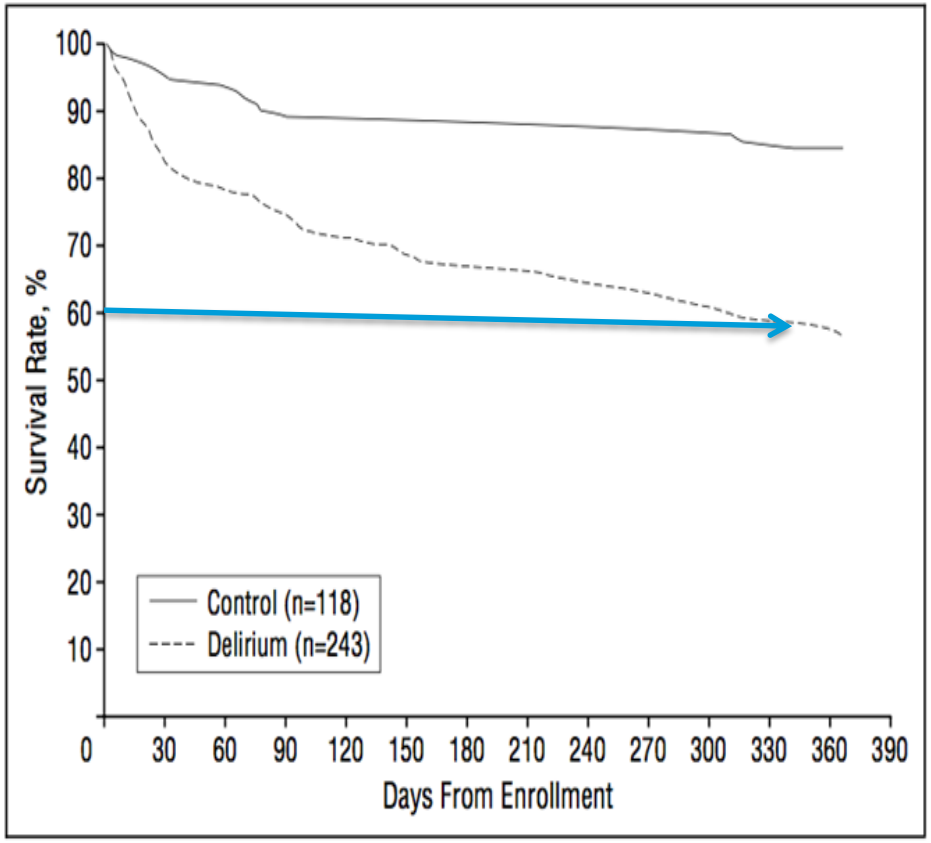


Figure 1. Unadjusted Kaplan-Meier survival curves of the 12-month mortality rate by study group.

The CAM-ICU

Confusion Assessment Method for the ICU (CAM-ICU) Flowsheet

1. Acute Change or Fluctuating Course of Mental Status:

- Is there an acute change from mental status baseline? OR
- Has the patient's mental status fluctuated during the past 24 h

YES

2. Inattention:

- *"Squeeze my hand when I say the letter 'A'."*
  Read the following sequence of letters: S A V E A H A A R T
  ERRORS: No squeeze with 'A' & Squeeze on letter other than
- If unable to complete Letters → Pictures

> 2 Errors

3. Altered Level of Consciousness

Current RASS level

RASS = zero

4. Disorganized Thinking:

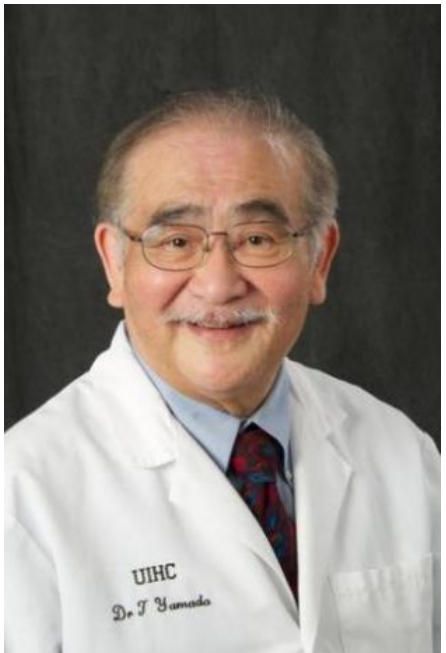
1. Will a stone float on water?
2. Are there fish in the sea?
3. Does one pound weigh more than two?
4. Can you use a hammer to pound a nail?

Command: "Hold up this many fingers" (Hold up 2 fingers)
"Now do the same thing with the other hand" (Do not de
OR "Add one more finger" (If patient unable to move both a

EEG and delirium

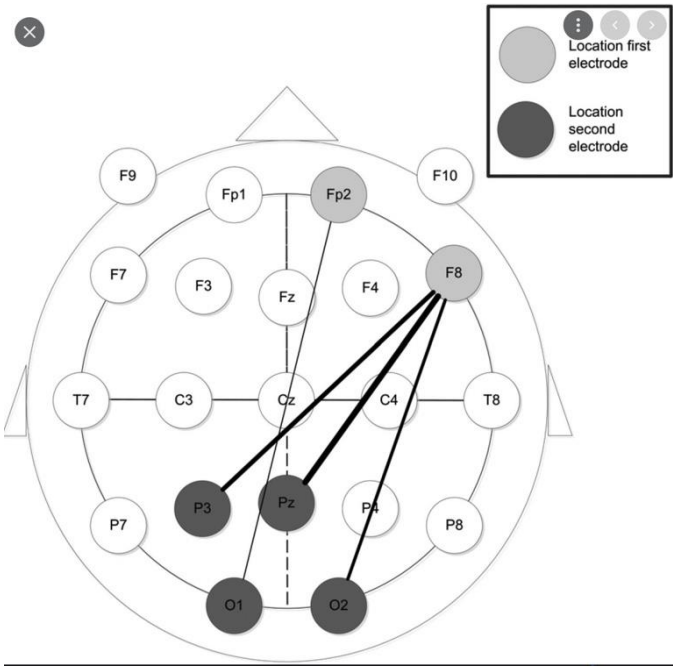
Traditional EEG

- Delirium can be detected by a traditional EEG
  - BUT, not practical for every pt even with high risk.
    - **Too big machine**
    - **Technician needed to place multiple leads**
    - **Neurology specialist to interpret**



EEG findings for delirium

- EEG findings are "**diffuse slowing**" =slow wave (delta~theta) **across all 20 leads**.
  - No need for 20 leads to detect diffuse slowing
  - Only a few leads are enough!
  - It is proven through systematic evaluation of many EEG pairs.



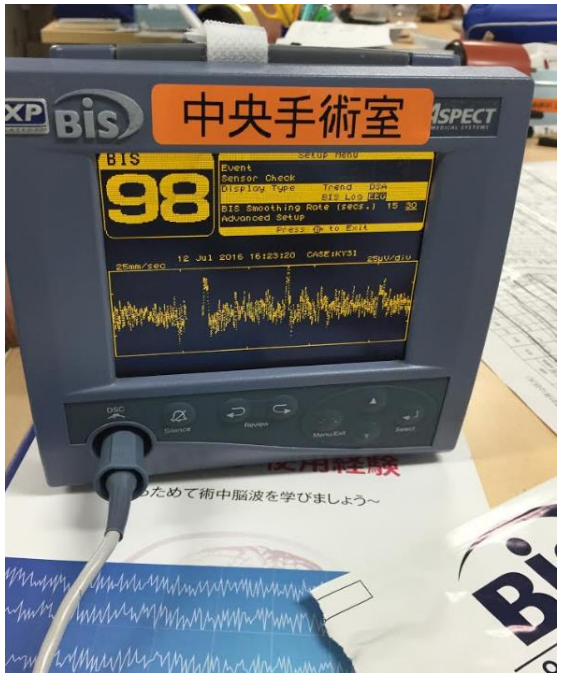
Van der Kooi, .. Slooter. Chest, 2015

Used in other areas

- Anesthesiology
  - Monitoring for depth of anesthesia
  - BIS monitor, Entropy etc
- ECT machine

  - Monitoring for seizure activities

BIS monitor



Delirium EEG Study

- To test if a simplified EEG device can detect delirium **among elderly high risk patients**.

- To test if a simplified EEG device can detect delirium **before clinical identification**.

20 leads versus 2 leads

versus

Study design and participants

- Study design prospective observational study, no intervention
  - Simple EEG device monitoring twice a day
  - Digital signal processing algorithm
  - DRS, DOSS and CAM-ICU twice a day
- Study population (2016~2019)
  - Initial two cohorts at high risk for delirium
    - **Orthopedic surgery** pts
    - **Older adult general medicine** pts

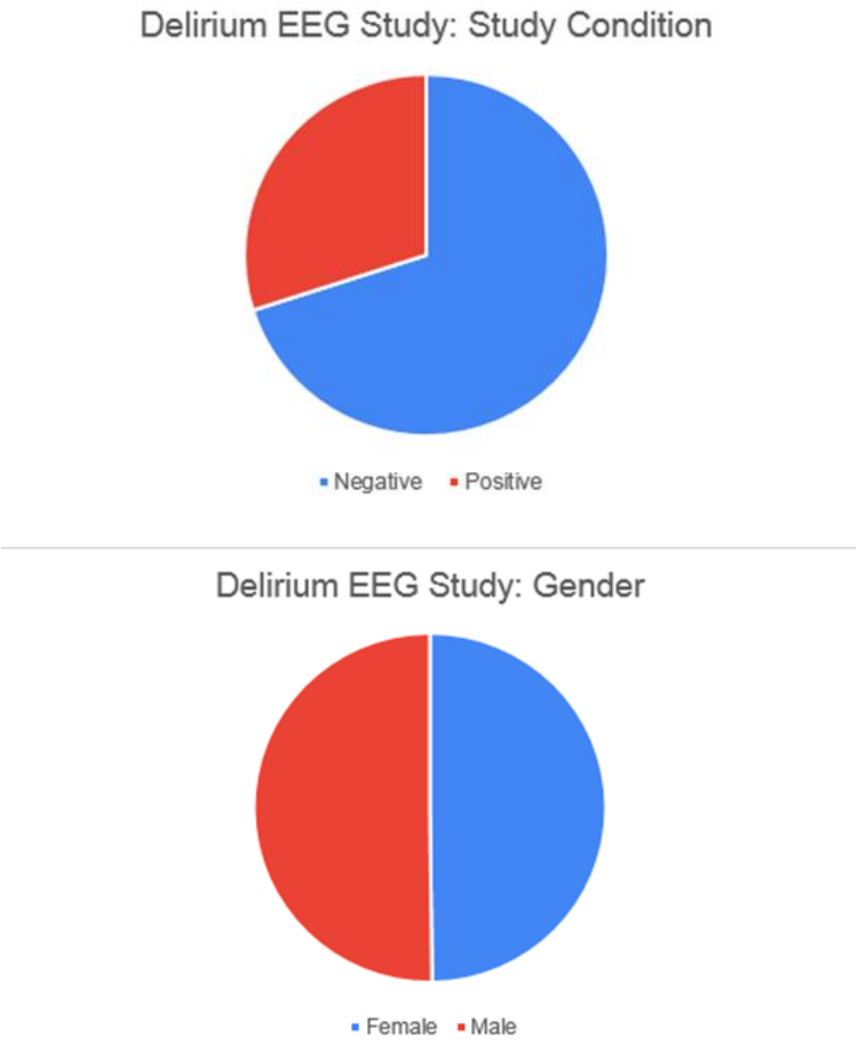
Demographics

- Total cases: 1307
  - Positive/Negative:

    391 (29.9%)/916 (70.1%)
    - Gen medicine: 67.8%
    - Orthopedics: 19.0%
    - ER: 16.3%
    - ICU: 4.3%
  - Female/Male:

    652 (49.9%) /655 (50.1%)
  - Average age:

    68.4 y.o. (SD: 13.8)

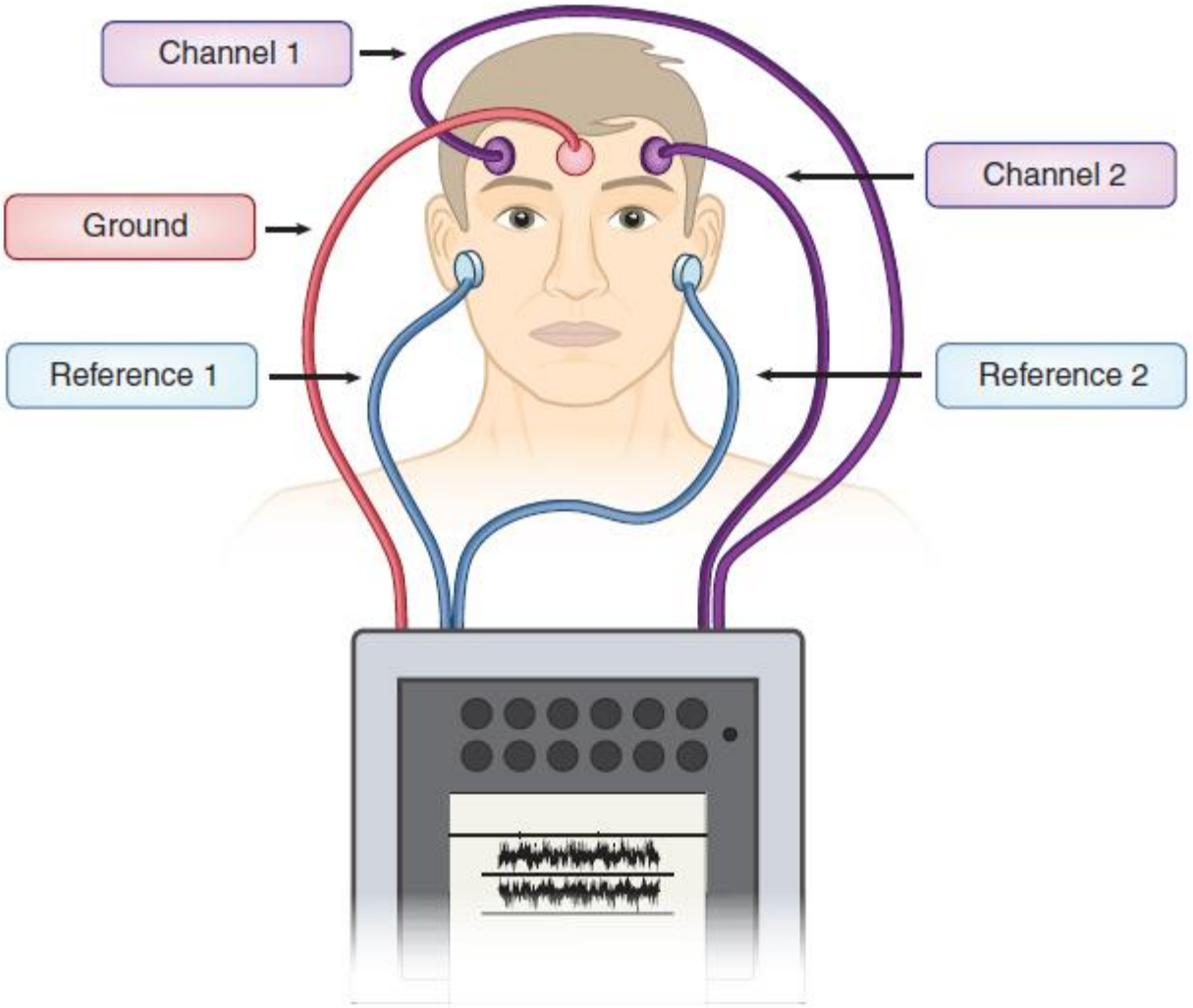


Our Device


A
A2
T4
O2
C4
Fp2
GND
A1
T3
O1
C3
Fp1
16:46
C3
C4
O1
O2
T3
T4
Start
Freeze
Back

A few electrodes on forehead

Electrode placement



Shinozaki et al. PCN 2018

EEG signals and spectral density analysis

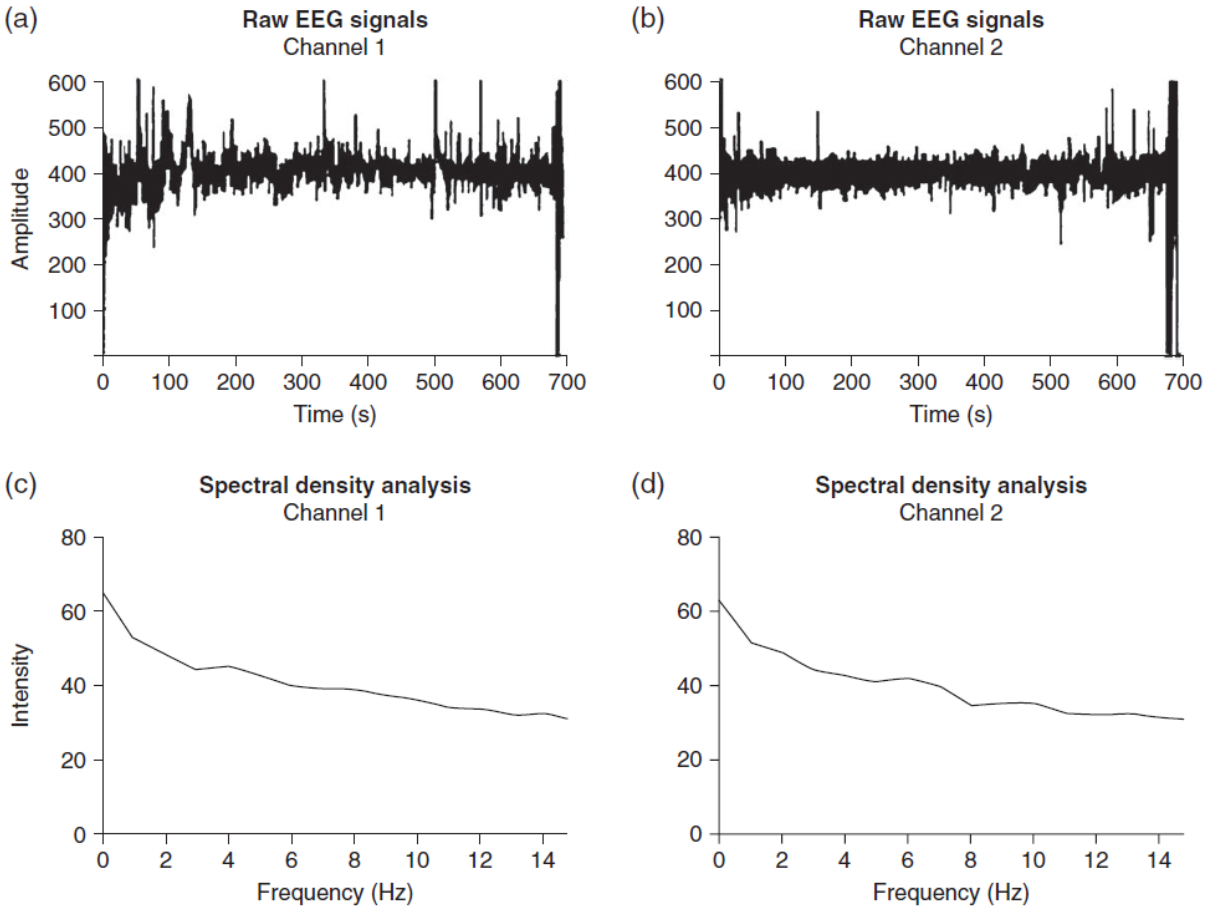
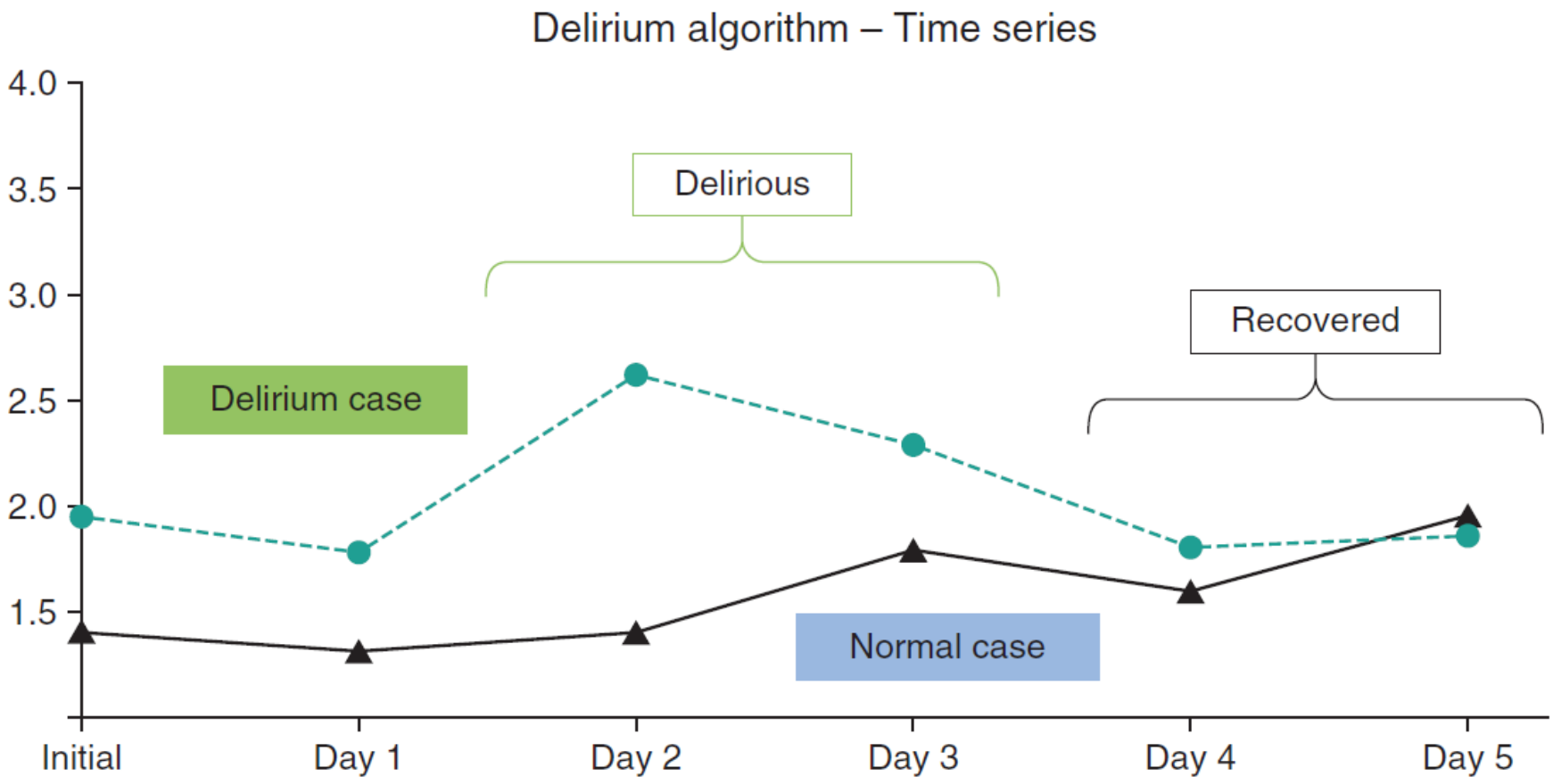


Figure 2. (a,b) Raw electroencephalography (EEG) signals over 10 min of recording. (c,d) Power spectral density analysis from the corresponding signal.

Shinozaki et al. PCN 2018

BSEEG score – Time series



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Initial group analysis from 45 cases

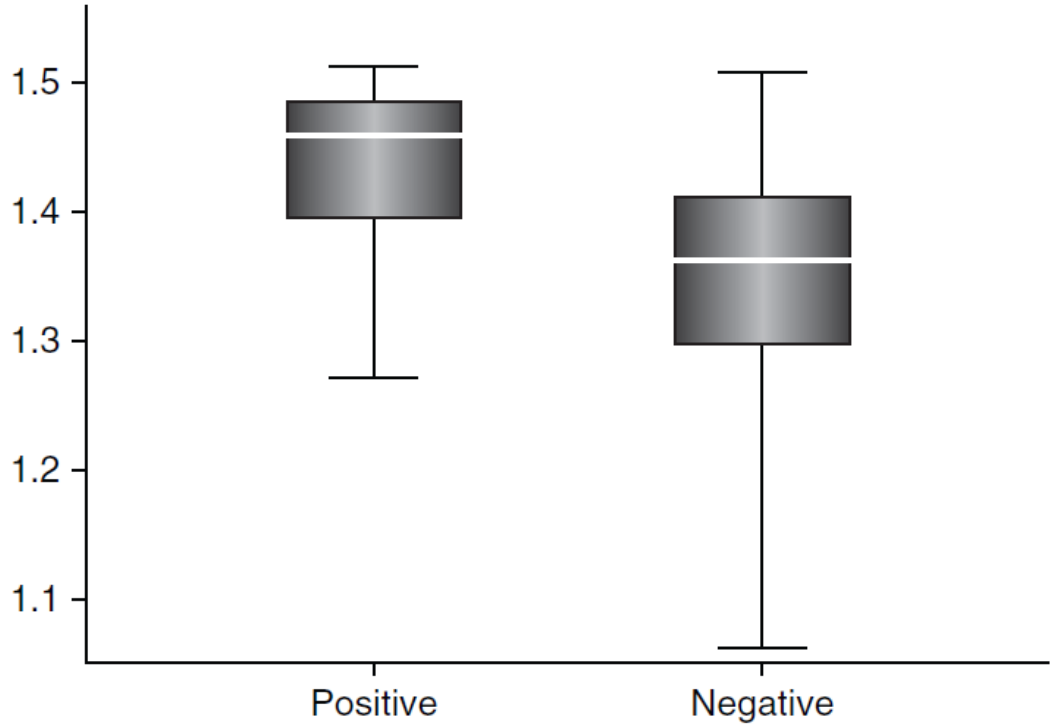


Figure 4. Data comparing electroencephalography scores based on power spectral density analysis between delirium cases (positive) and normal controls (negative) from a total of 45 subjects. By selecting a cut-off score of 1.44, the two groups were distinguished with an accuracy of 87.5%.

Shinozaki et al. PCN 2018

ROC analysis from test dataset

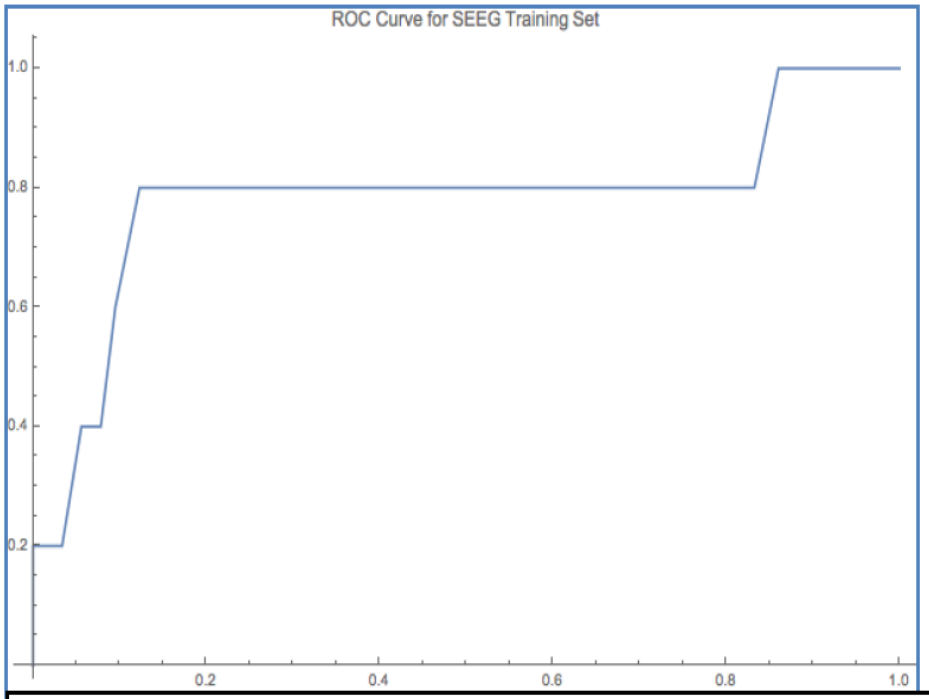


Figure 3: ROC of test data set. AUC was ~0.7 with this dataset. Although it is close to what we are aiming for, validation with larger and independent dataset is needed.

We chose BSEEG score 1.44 as cut off.
Positive >1.44,
negative <1.44

N=45
Accuracy 88%
Sensitivity 80%
Specificity 88%
AUC=0.70

Shinozaki et al. PCN 2018

Validation 1 from Inpatient

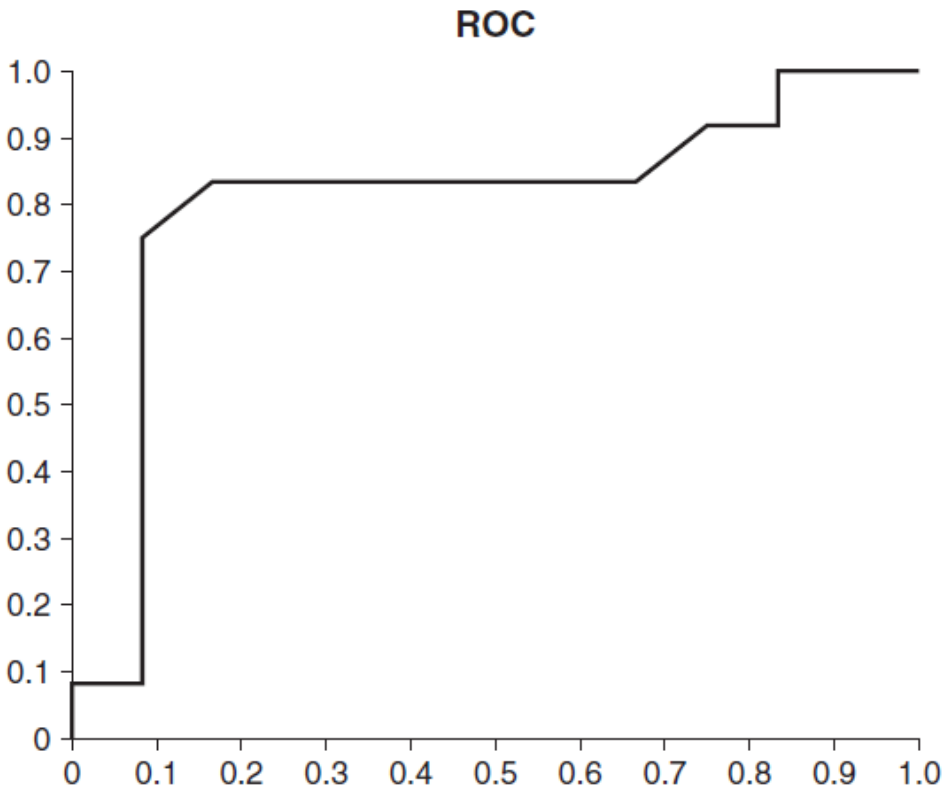


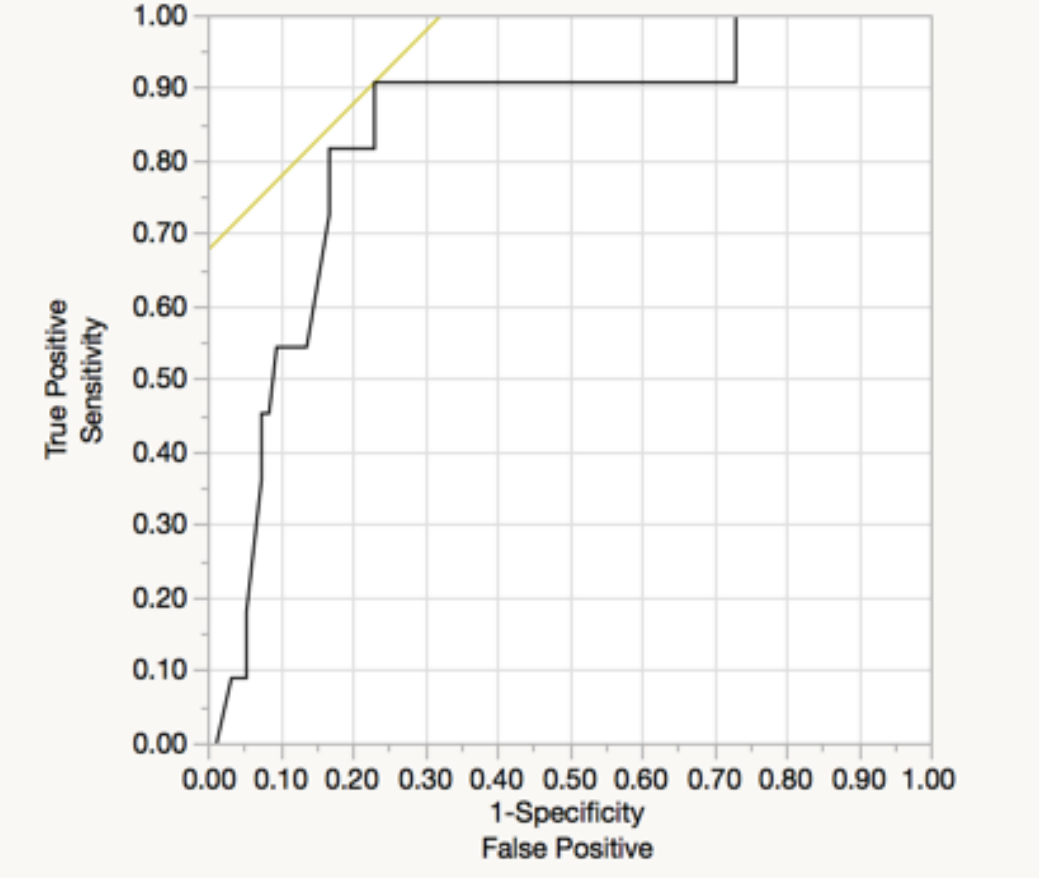
Figure 5. Receiver–operator curve (ROC) from the validation dataset. The area under the curve was 0.805.

	Delirium Positive	Delirium Negative
EEG score positive	10	2
EEG score negative	2	10

N=24
Sensitivity 83%
Specificity 83%
AUC=0.81

Shinozaki et al. PCN 2018

Validation 2 from ER

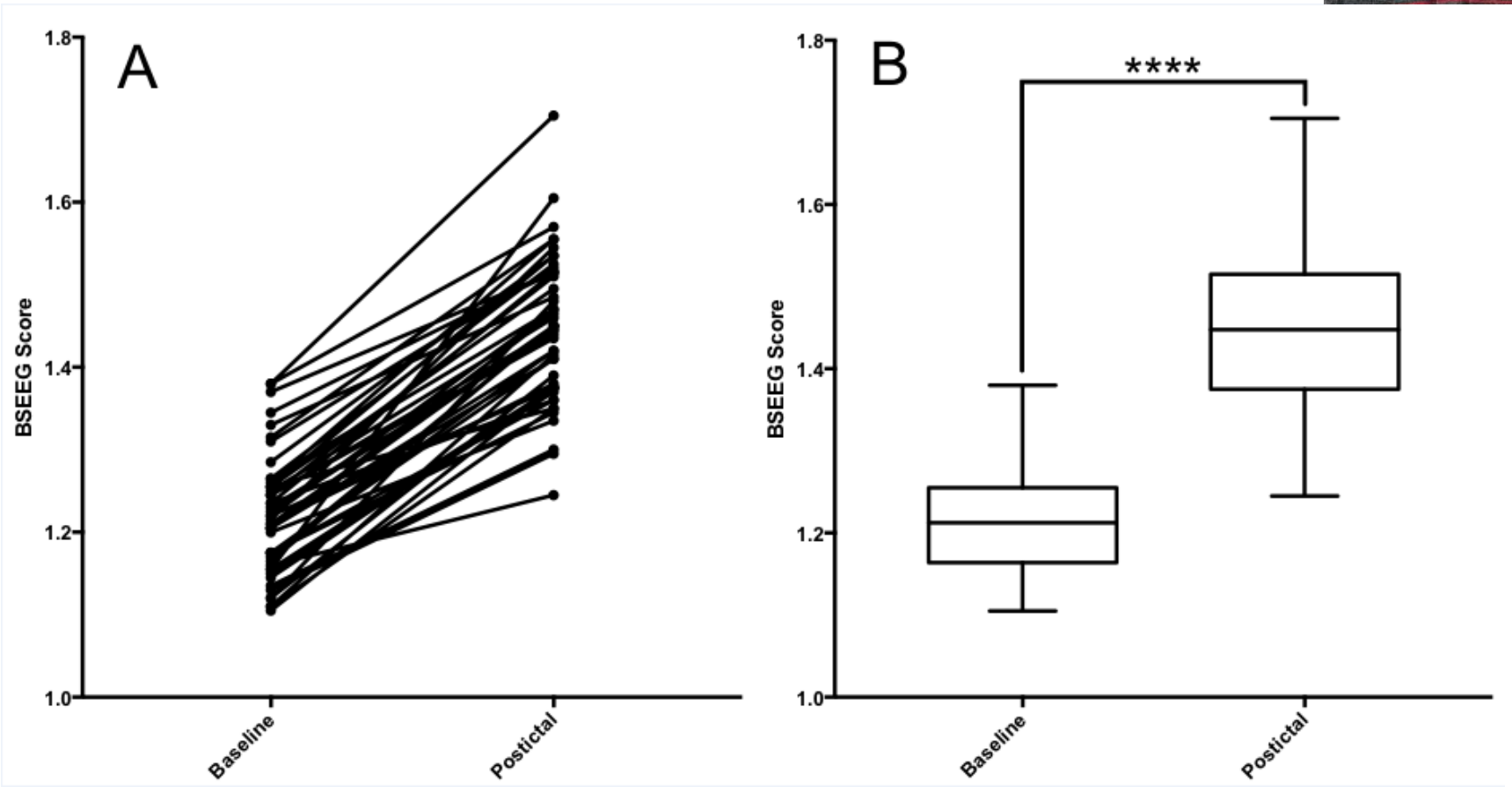


	Delirium Positive	Delirium Negative
EEG score positive	10	24
EEG score negative	1	80

N=115
Sensitivity 91%
Specificity 77%
AUC=0.84

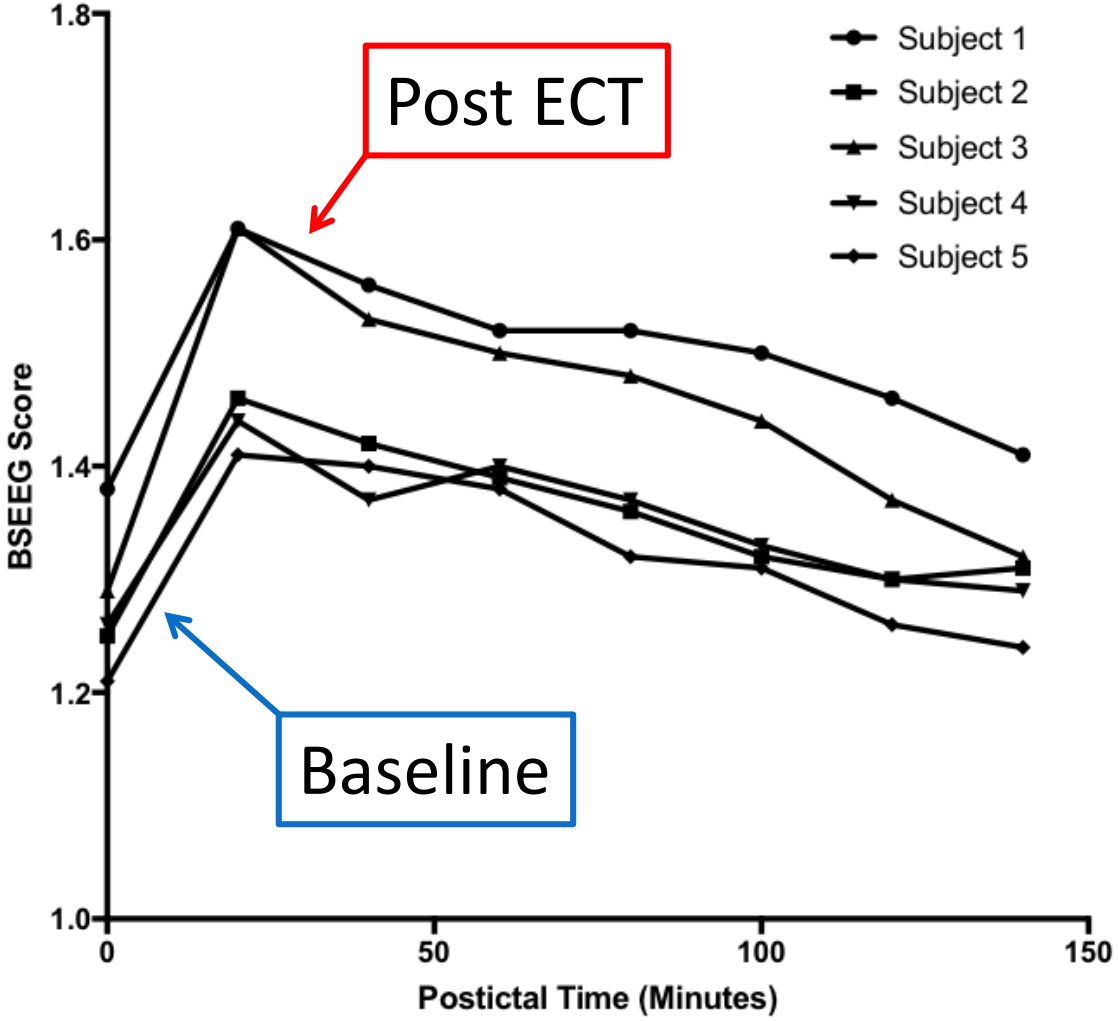
Lee et al. AJEM 2018

Validation 3 from ECT
Before and after ECT



Zarei et al. Psychiatry Research 2020

ECT case monitoring over 2 hours



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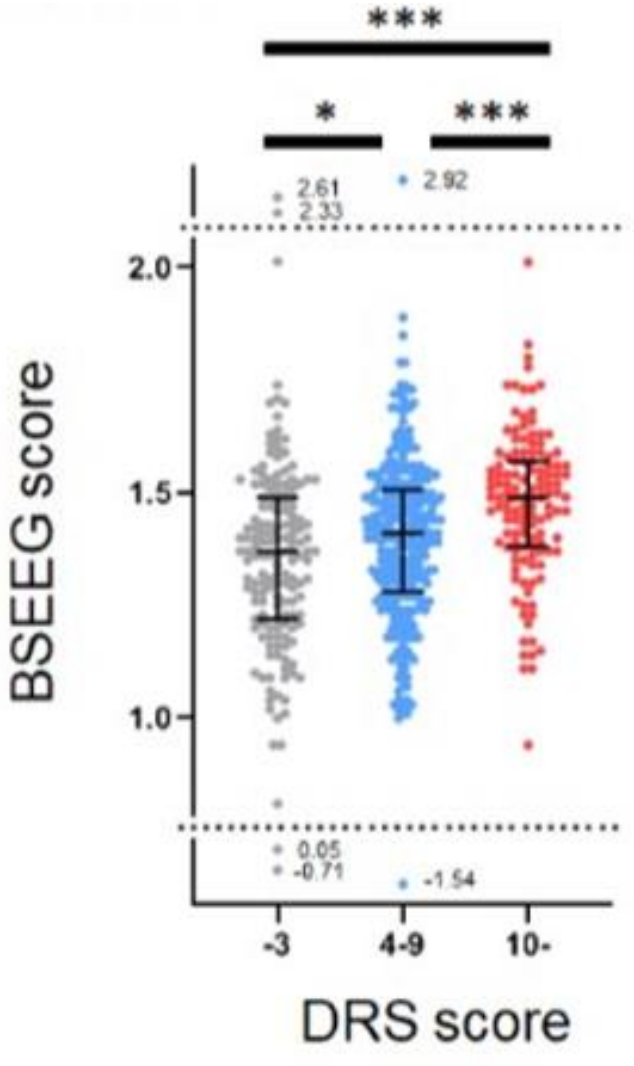
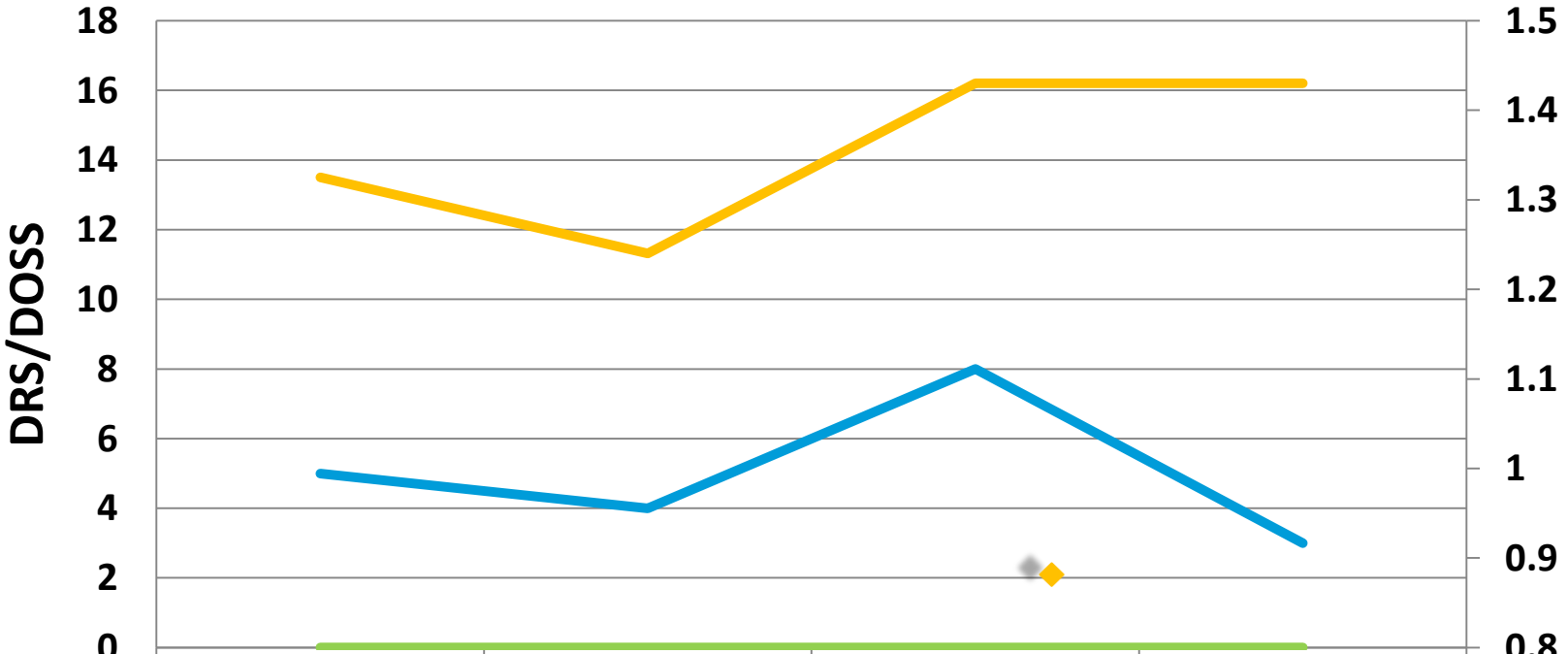
New device tested

Validation 5 with a new device
BSEEG score can quantify severity



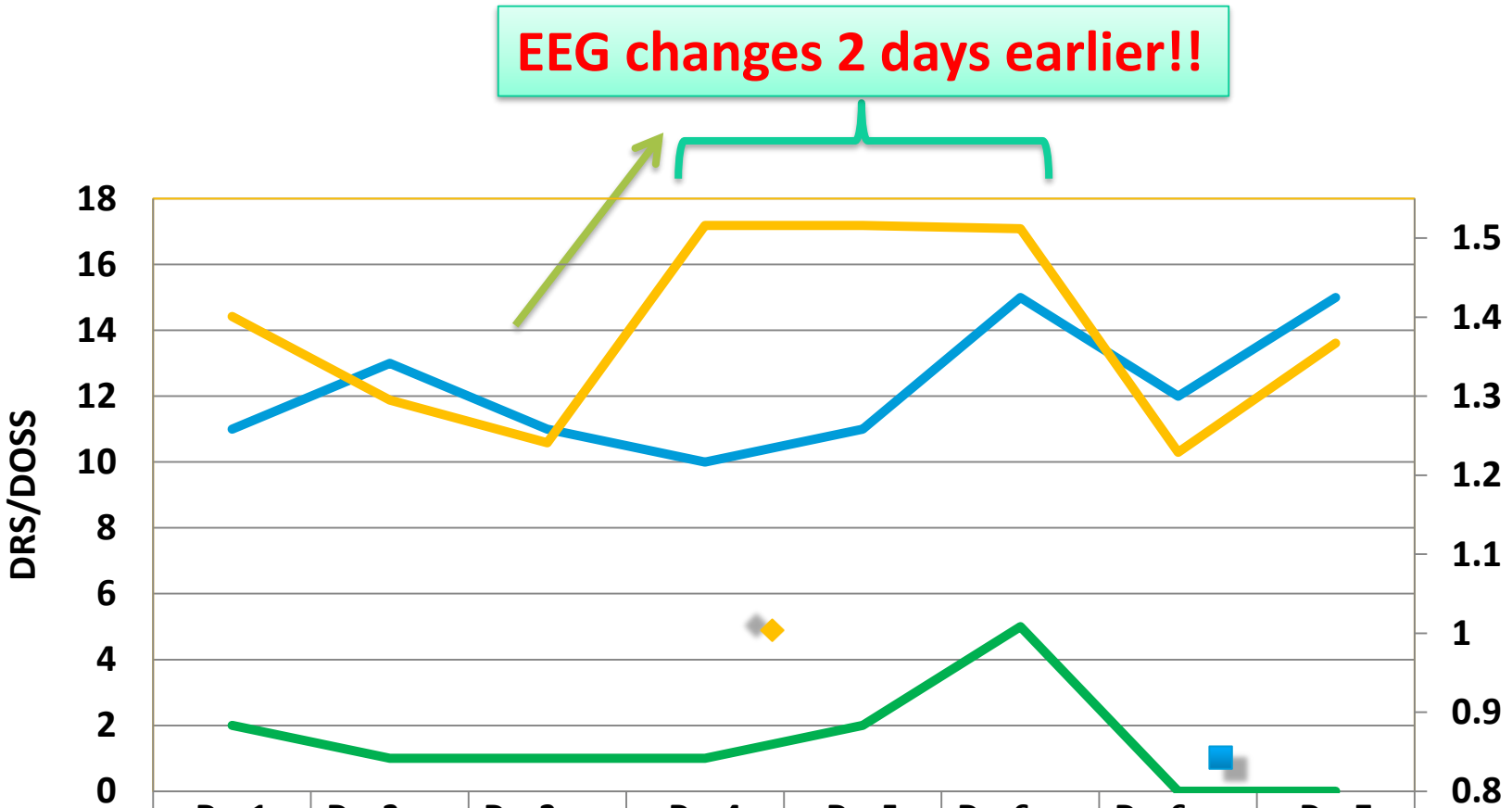
Yamanashi et al. under review

Can EEG predict delirium onset? Negative case



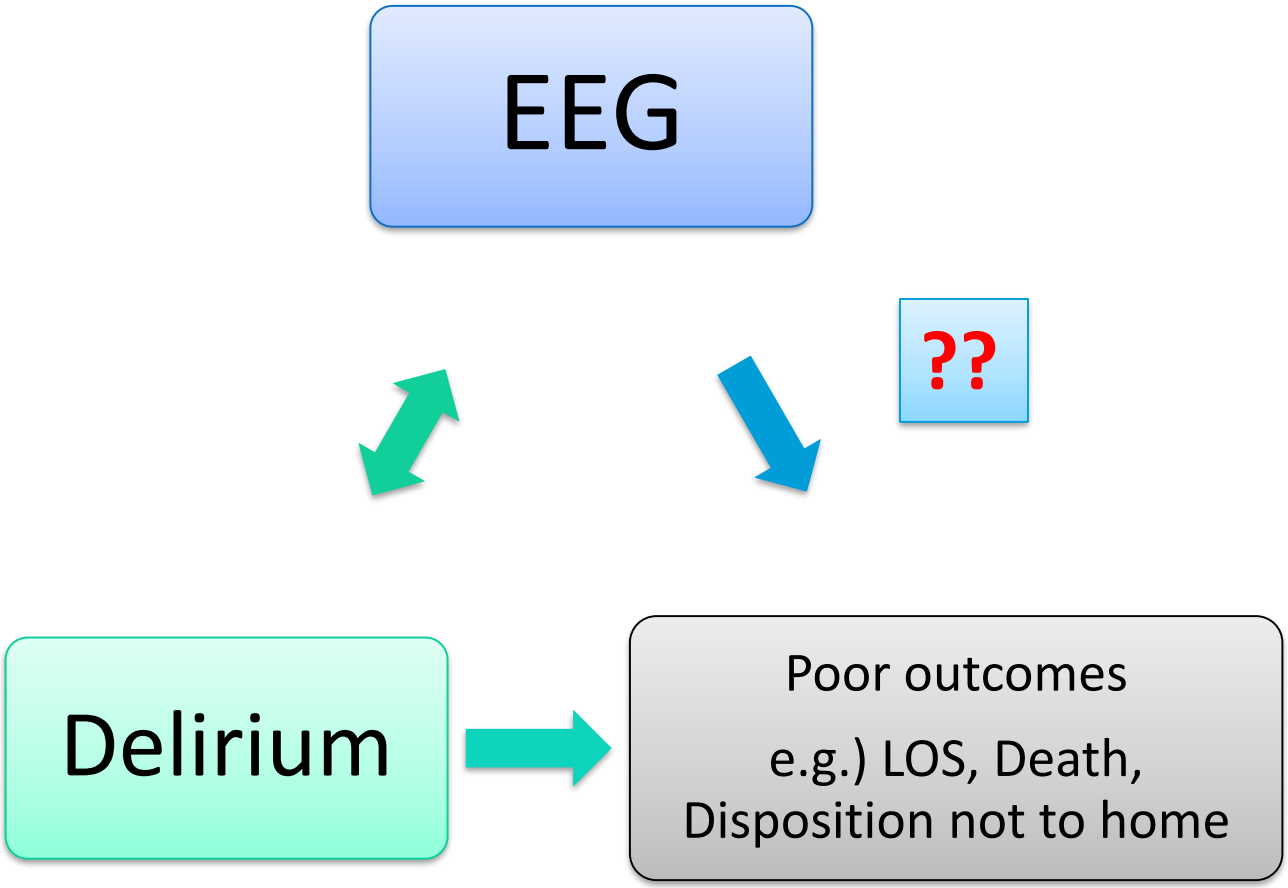
	Day1	Day2 am	Day2 pm	Day3
DRS	5	4	8	3
DOSS	0	0	0	0
EEG	1.325	1.24	1.43	1.43

Can EEG predict delirium onset? Positive case



	Day1	Day2 am	Day2 pm	Day4	Day5	Day6 am	Day6 pm	Day7
DRS	11	13	11	10	11	15	12	15
DOSS	2	1	1	1	2	5	0	0
EEG	1.401	1.295	1.241	1.516	1.516	1.512	1.229	1.367

Delirium, poor outcomes, and EEG



Outcomes and BSEEG score

- LOS and BSEEG scores were significantly correlated.
  - *P* = 0.0010, unadjusted
  - *P* = 0.0014, adjusted for age, gender and CCI

- Discharge outcome and BSEEG scores were significantly associated.
  - *P* = 0.0038, unadjusted
  - *P* = 0.0090, adjusted for age, gender, and CCI

Shinozaki et al. J of Clin Psych 2019

Delirium and mortality (Arch Int Med 2002)

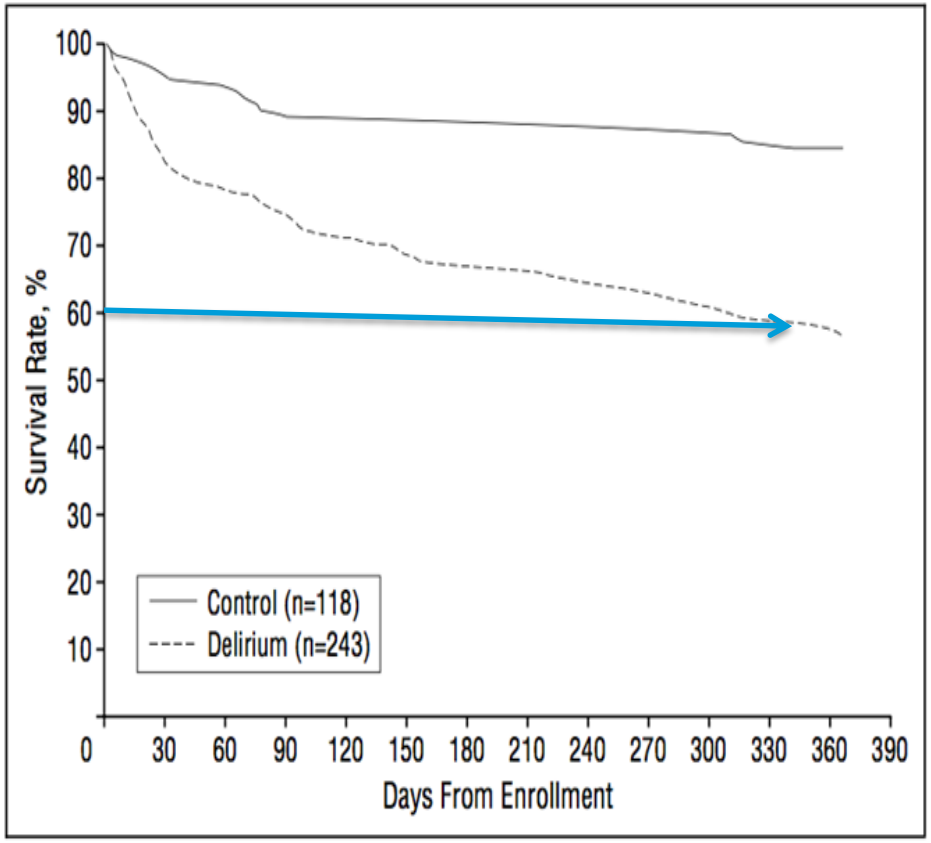
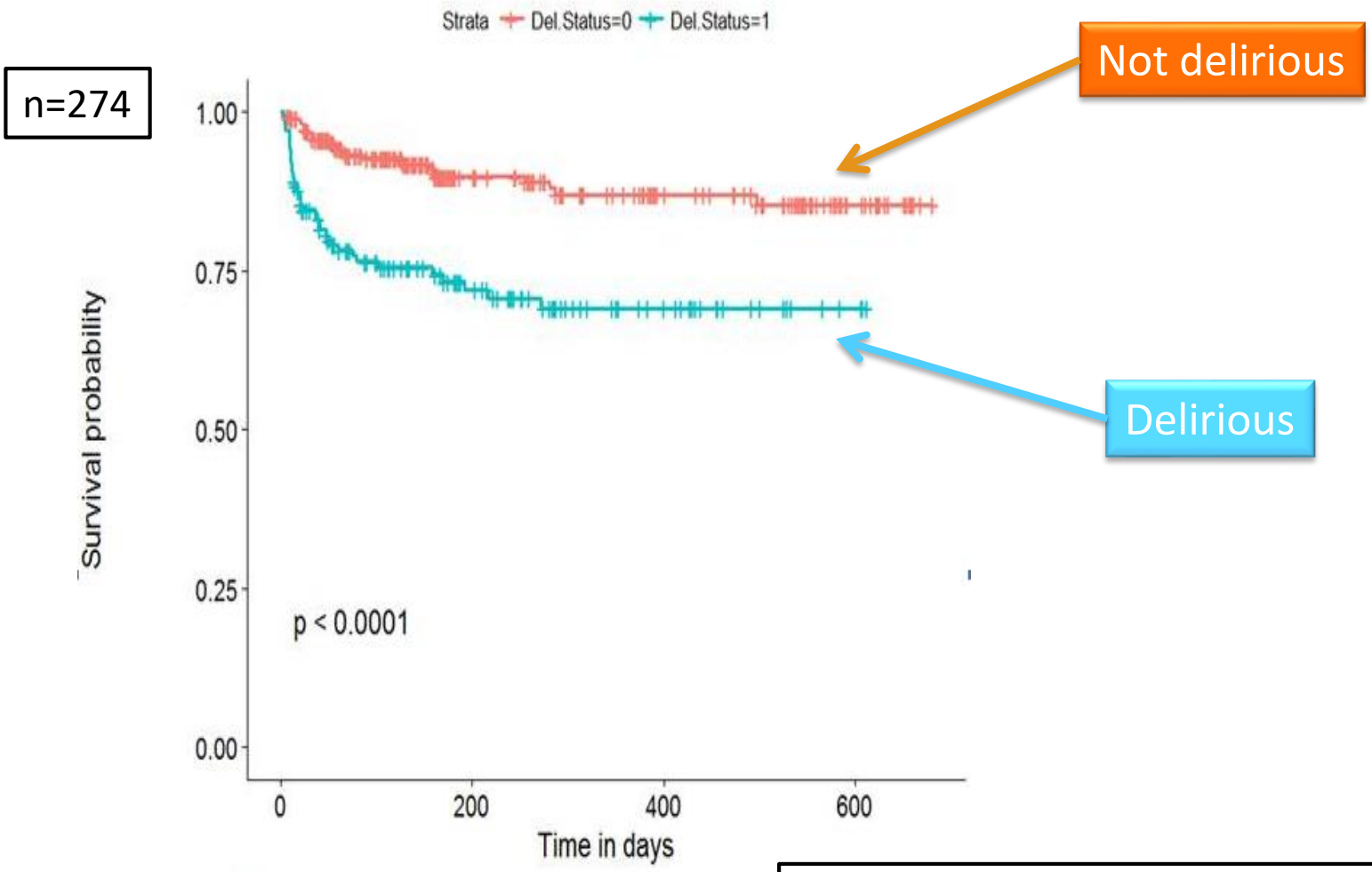


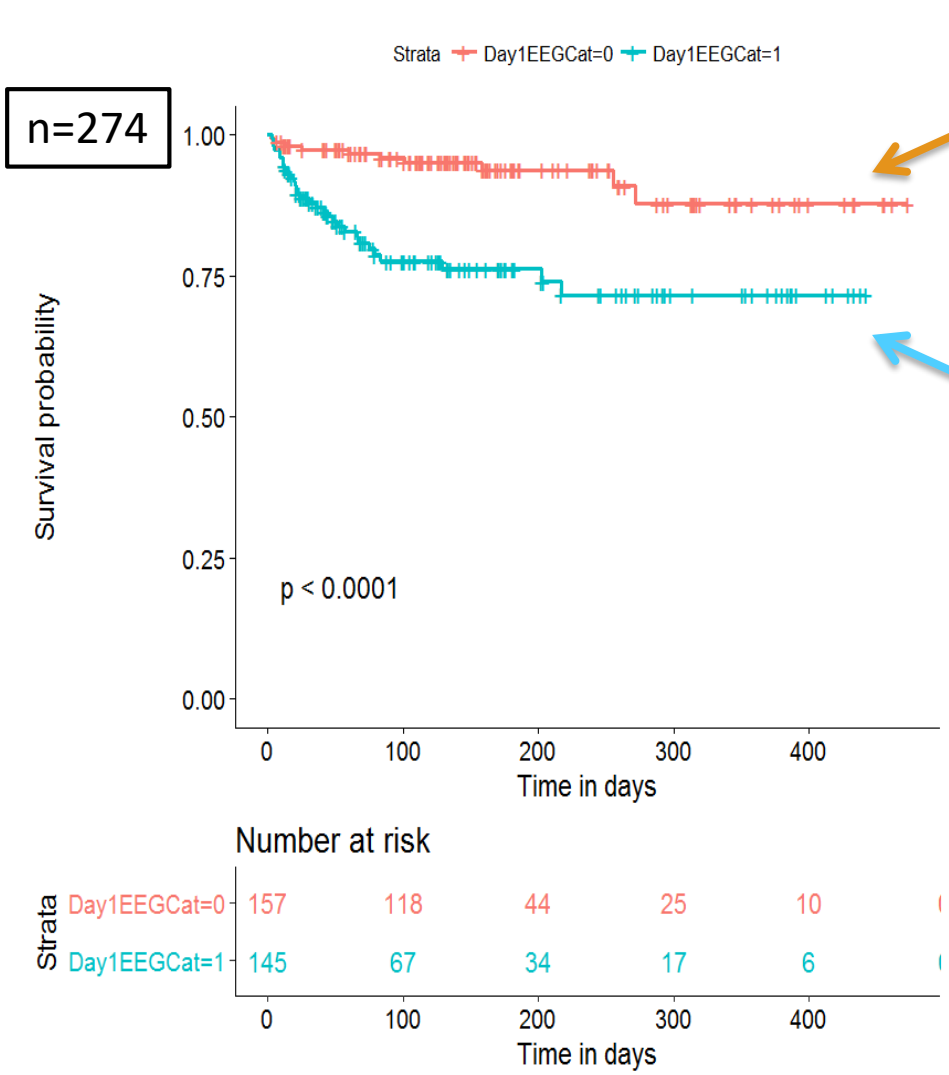
Figure 1. Unadjusted Kaplan-Meier survival curves of the 12-month mortality rate by study group.

Delirium and mortality (our data)



Shinozaki et al. J of Clin Psych 2019

Can EEG predict Mortality?



BSEEG low

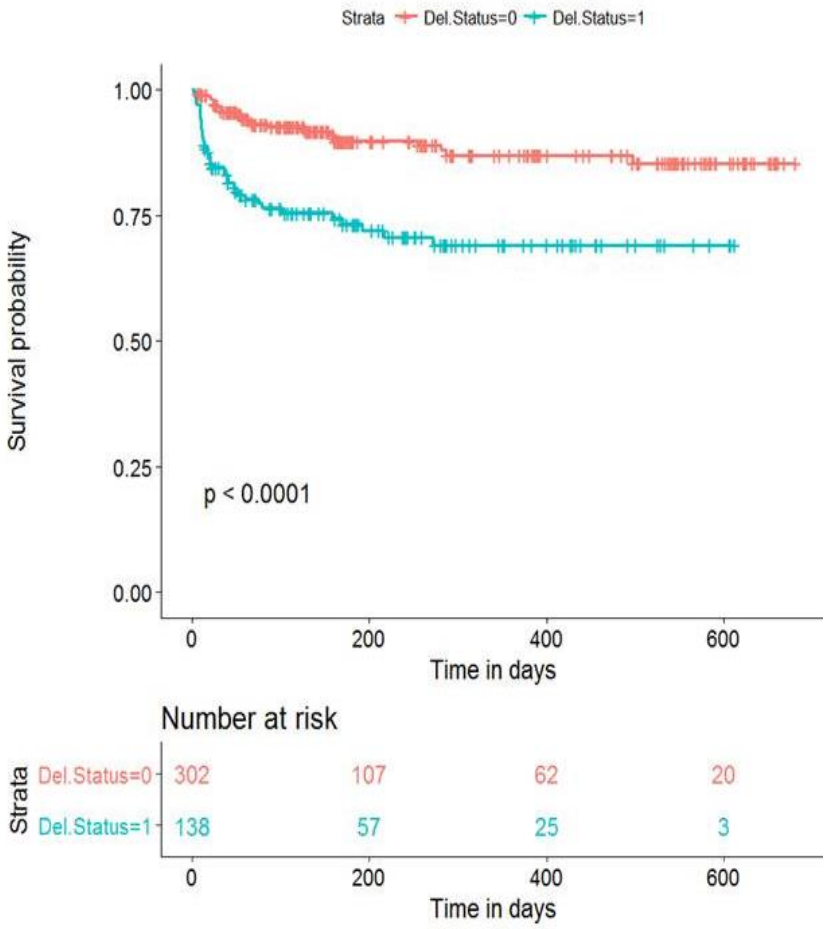
BSEEG high

- lm(formula = Survival ~ Day1EEG)
  - Day1EEG p = 0.00951 **
- lm(formula = Survival ~ Day1EEG + CCI.Score)
  - Day1EEG p = 0.03835 *
  - CCI.Score p = 0.00227 **

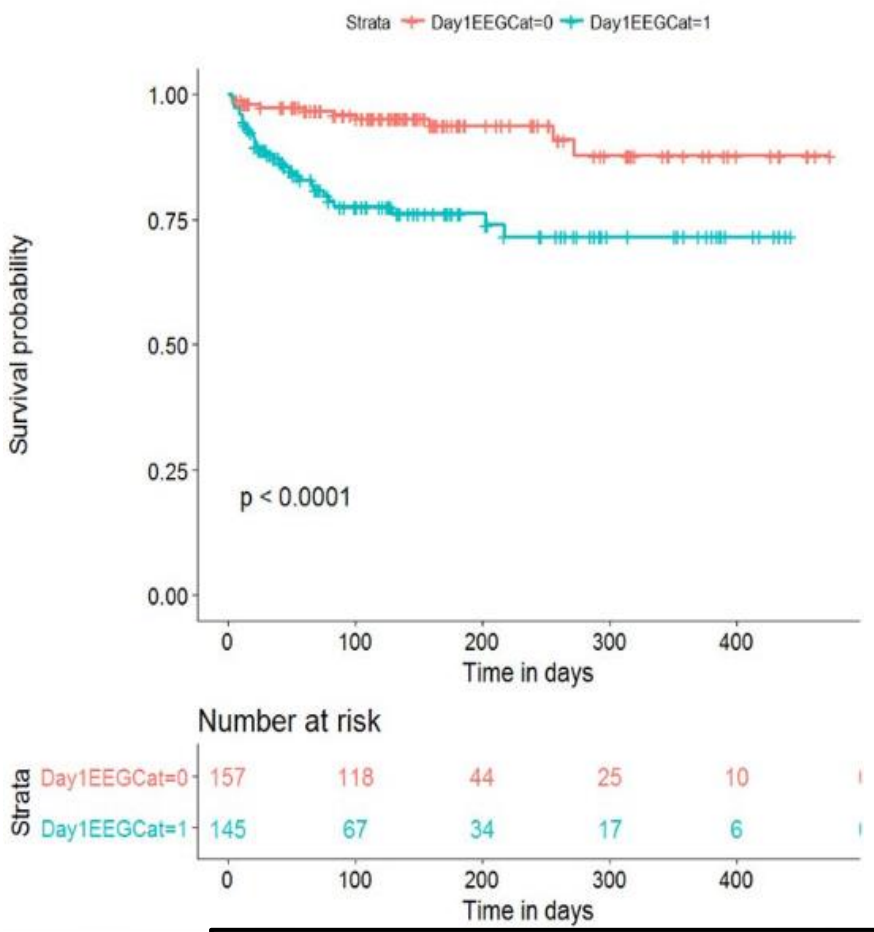
Shinozaki et al. J of Clin Psych 2019

Power of objective phenotyping

Clinical category



EEG category



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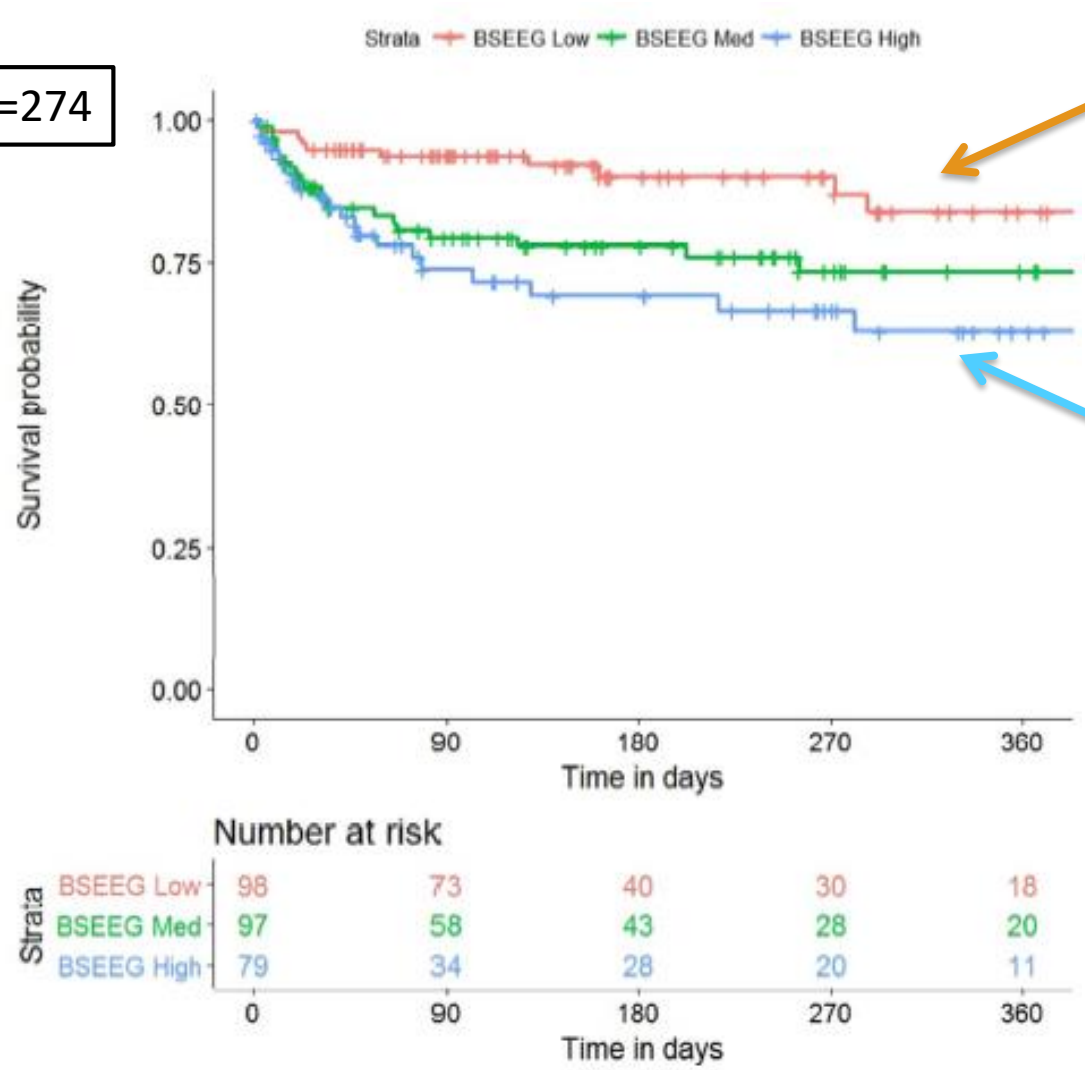
Dose dependent effect

n=274



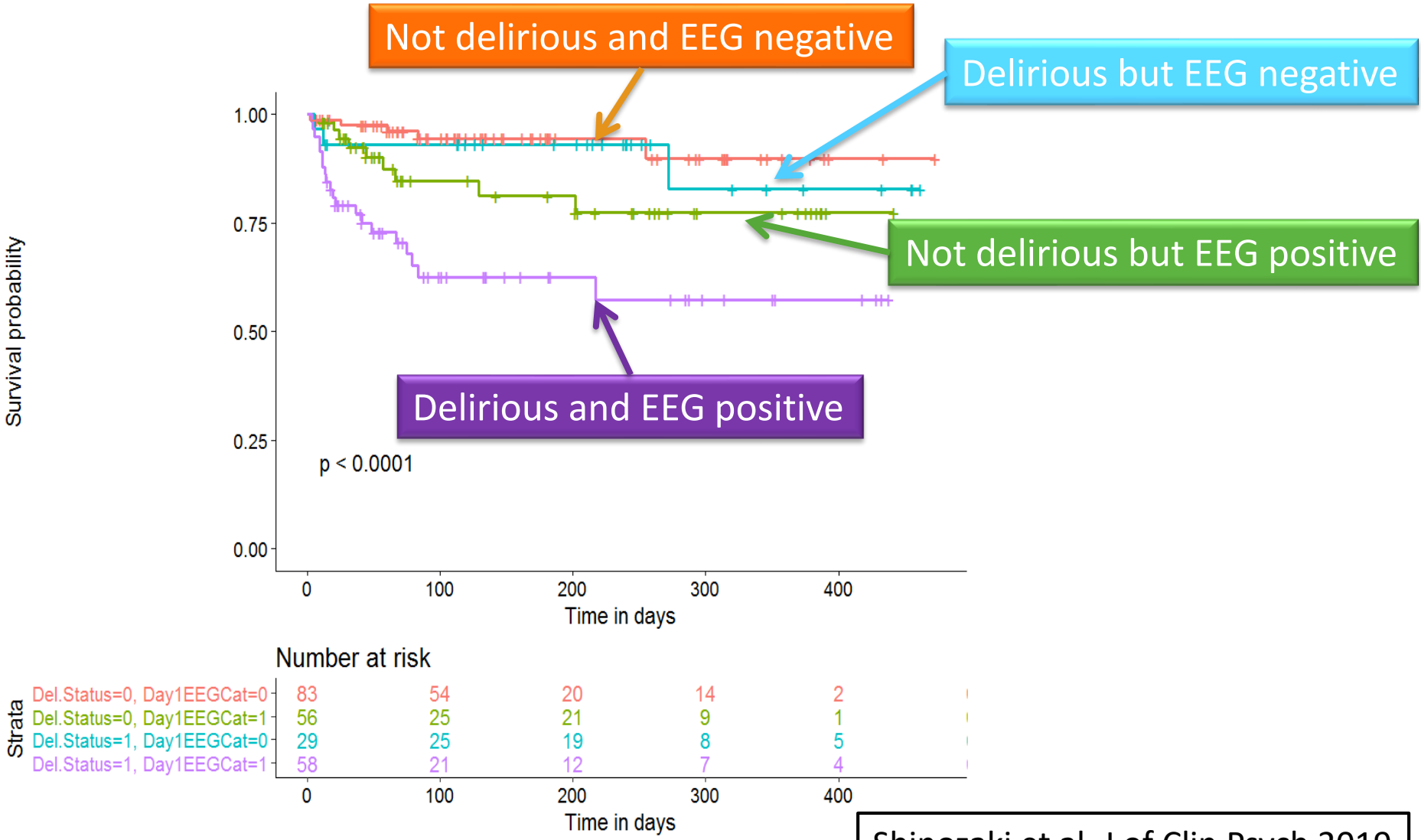
BSEEG low

BSEEG middle

BSEEG high

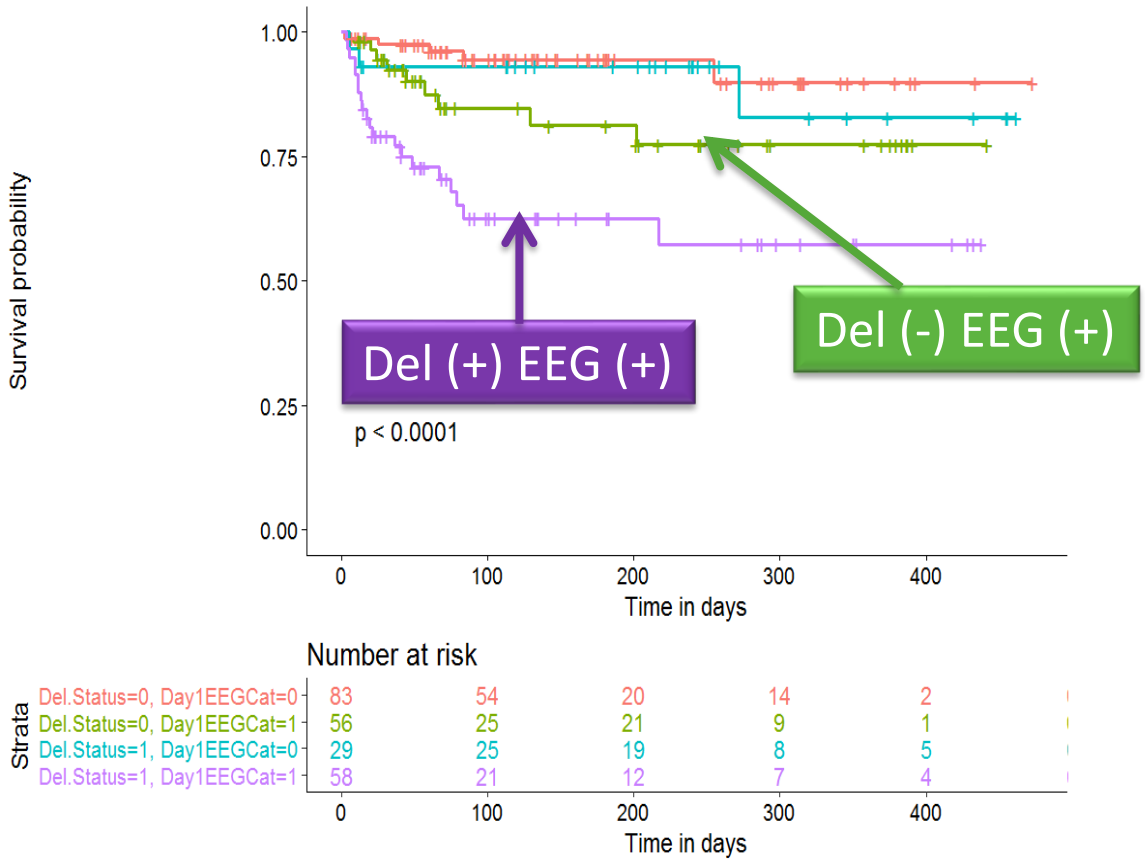
Shinozaki et al. J of Clin Psych 2019

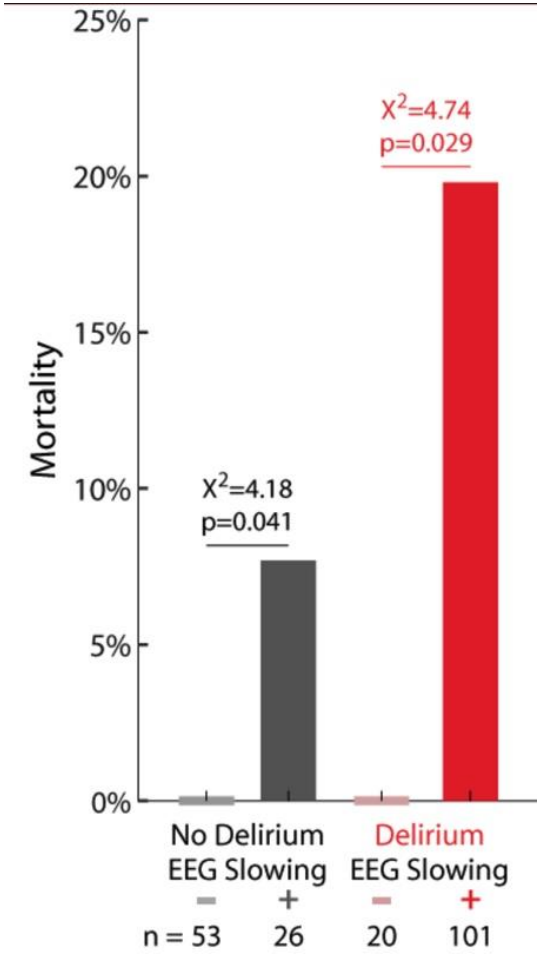
EEG x Delirium category and Mortality



Shinozaki et al. J of Clin Psych 2019

Consistent with hospital mortality = EEG matters!!





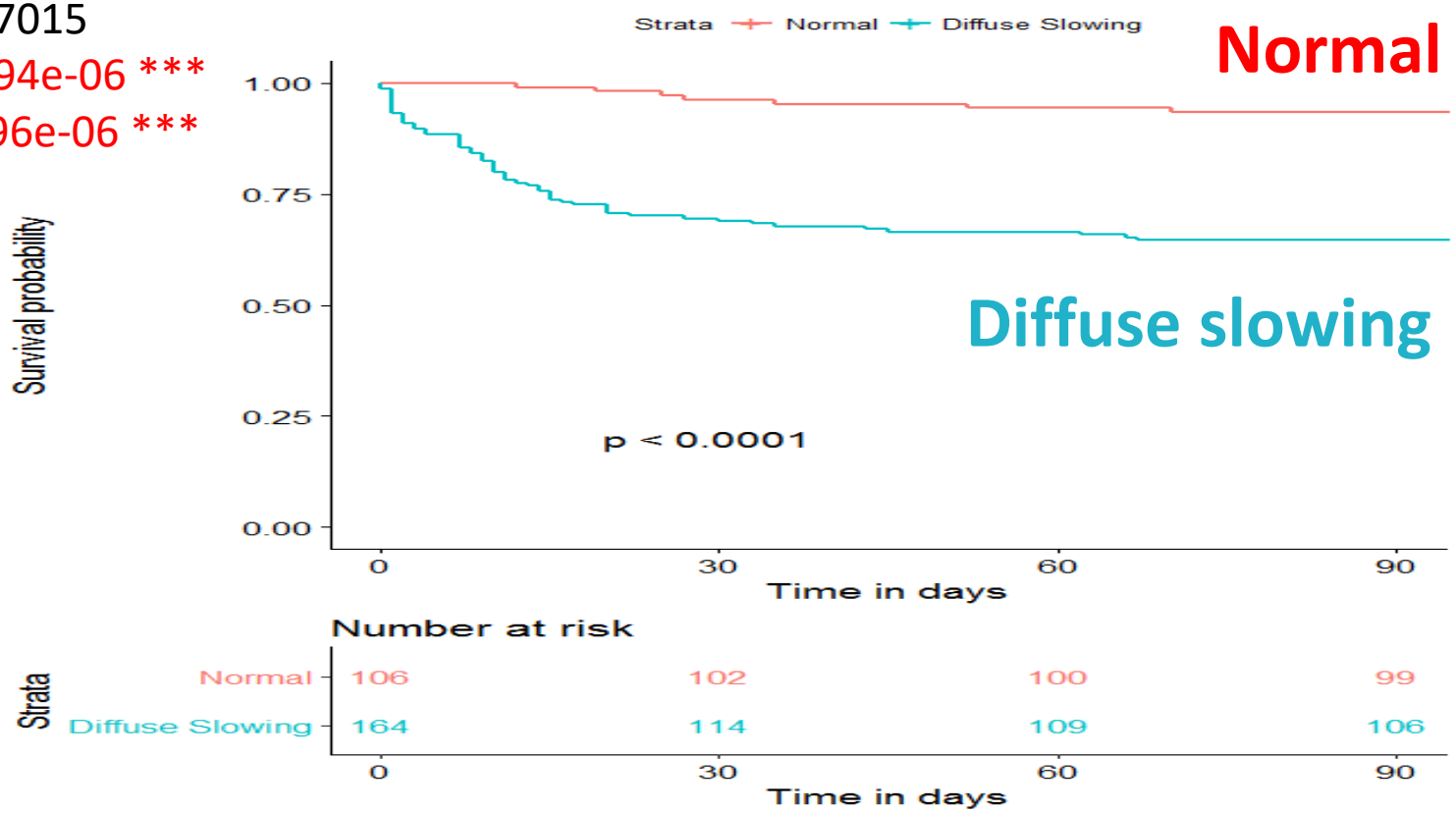
Shinozaki et al. J of Clin Psych 2019

Kimchi et al. Neurology 2019

“Diffuse slowing” in EEG finding and mortality

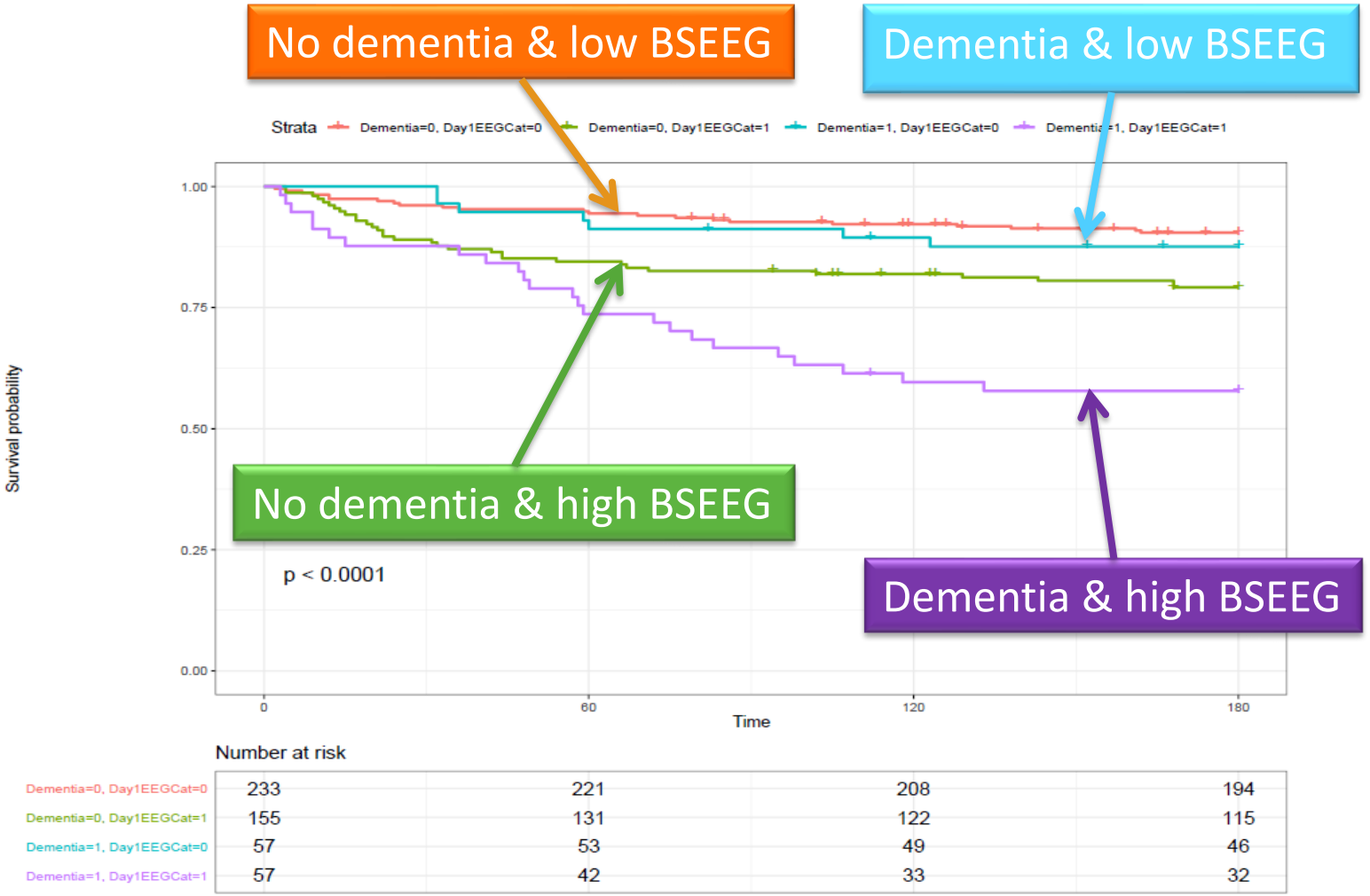
glm(formula = as.numeric(Censor) ~ Sex + Age + CCI + slowing)

(Intercept)	0.0161 *
Sex	0.9396
Age	0.7015
CCI	3.94e-06 ***
slowing	1.96e-06 ***



Wanzek et al. Ann Clin Psych 2021

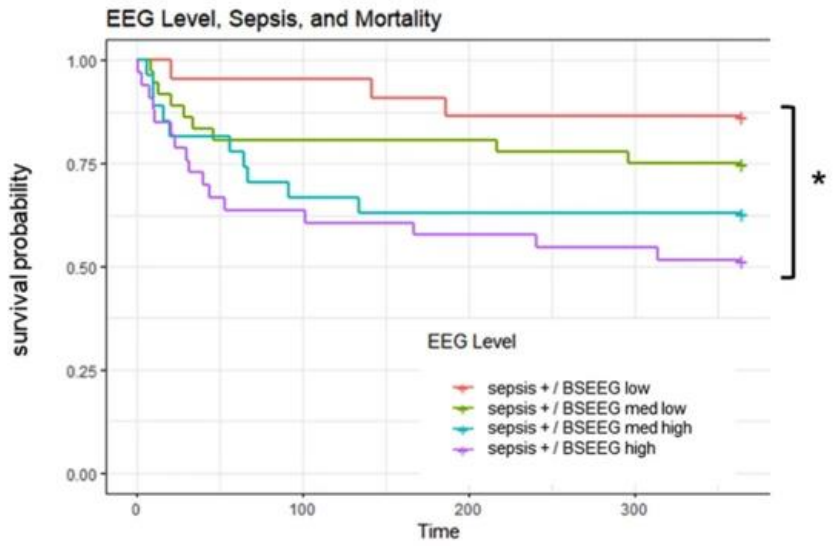
Dementia and BSEEG



Saito et al. 2021
Brain Communications

Sepsis and BSEEG

(A)

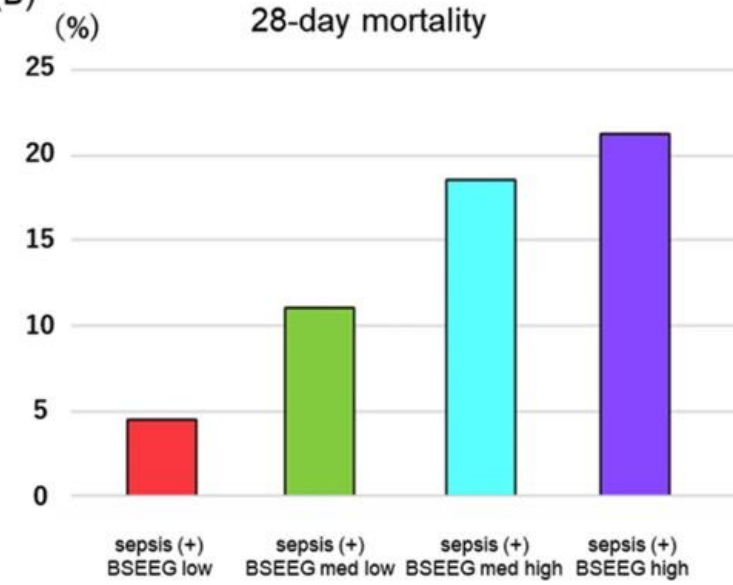


Number at risk

					survival rate	95% CI
sepsis + / BSEEG low	22	21	19	19	0.864	0.634-0.954
sepsis + / BSEEG med low	36	29	29	27	0.750	0.575-0.861
sepsis + / BSEEG med high	27	18	17	17	0.630	0.421-0.781
sepsis + / BSEEG high	33	21	19	18	0.515	0.335-0.669

p=0.03

(B)

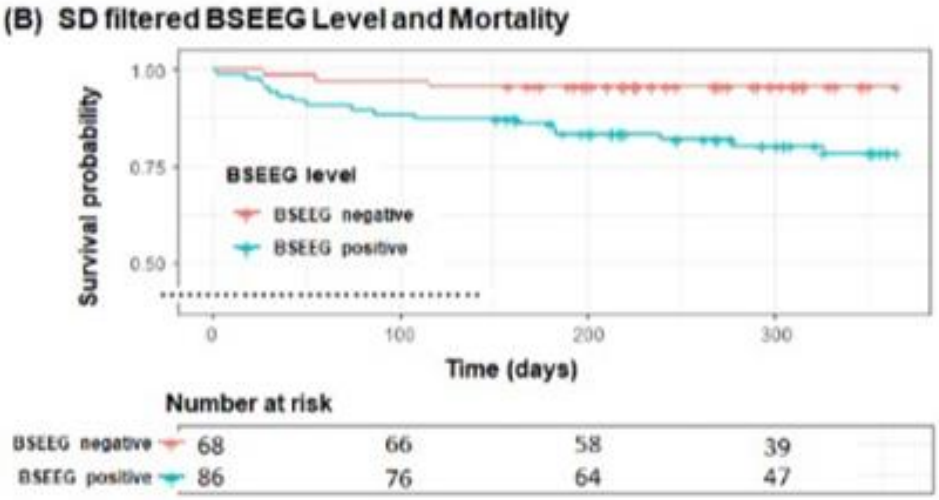


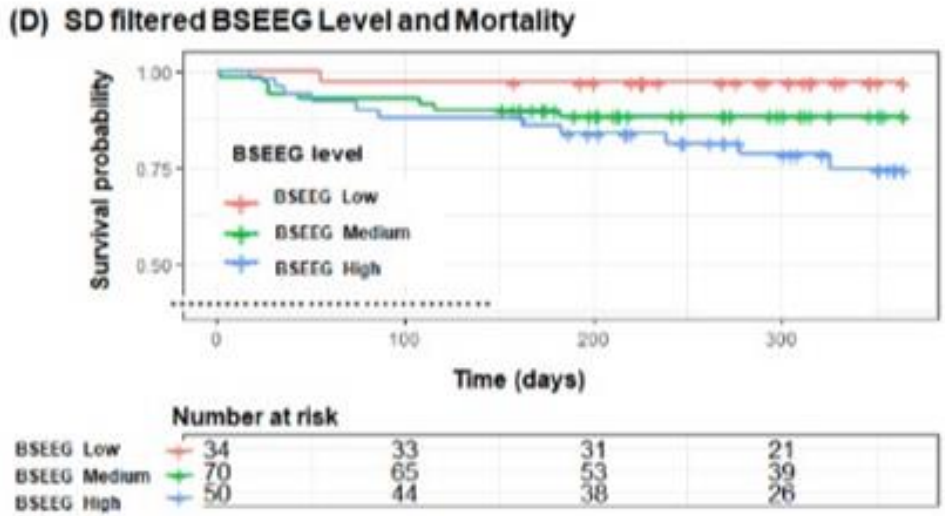
logistic regression	OR	95% - CI	p-value
BSEEG grouping			
low	1.00	reference	
med low	2.62	0.27 - 25.1	0.40
med high	4.77	0.51 - 44.3	0.17
high	5.65	0.64 - 49.6	0.12

Yamanashi et al. 2021
Scientific Reports

Another replication with a new device

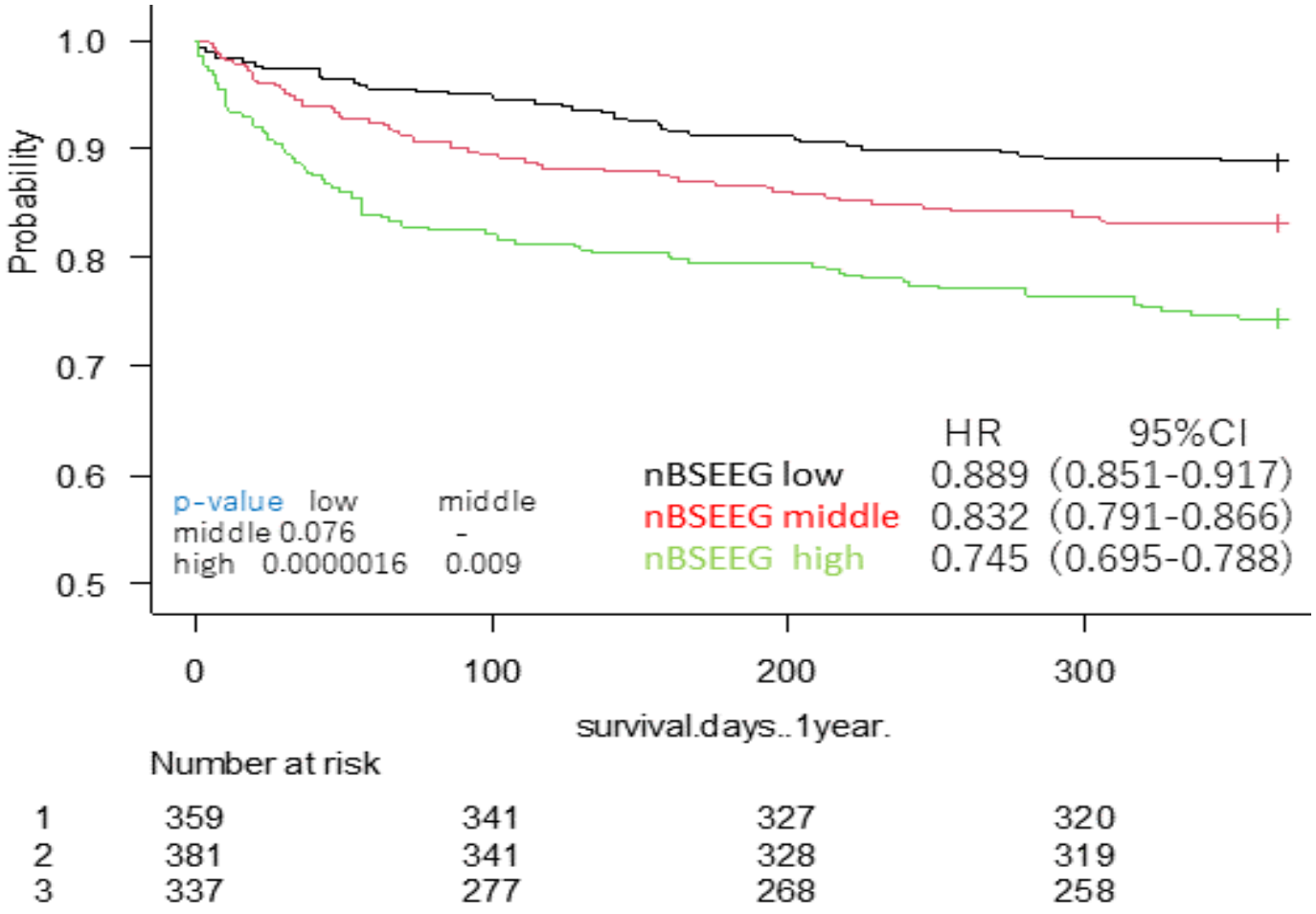
n=154
Third
cohort

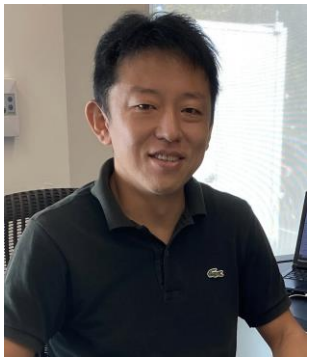




Yamanashi, Crutchley et al.
BJP 2021

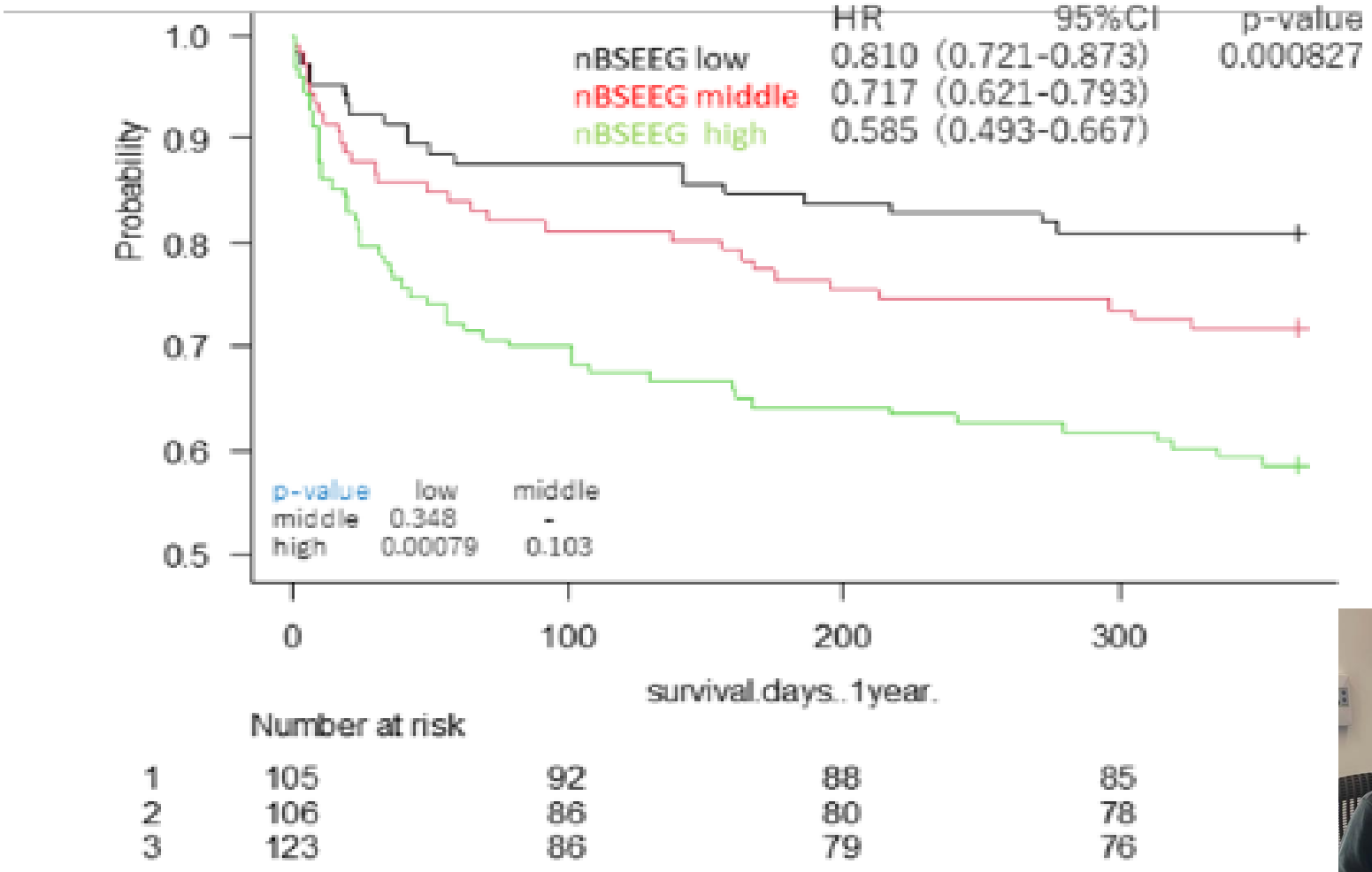
Validated with 1,077 subjects

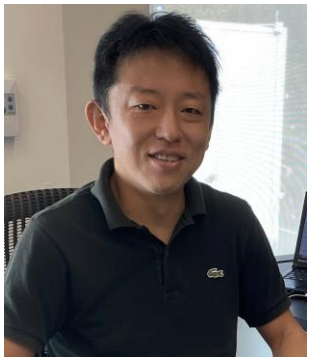




Nishizawa et al. AJGP 2023

All delirious patients are not the same.





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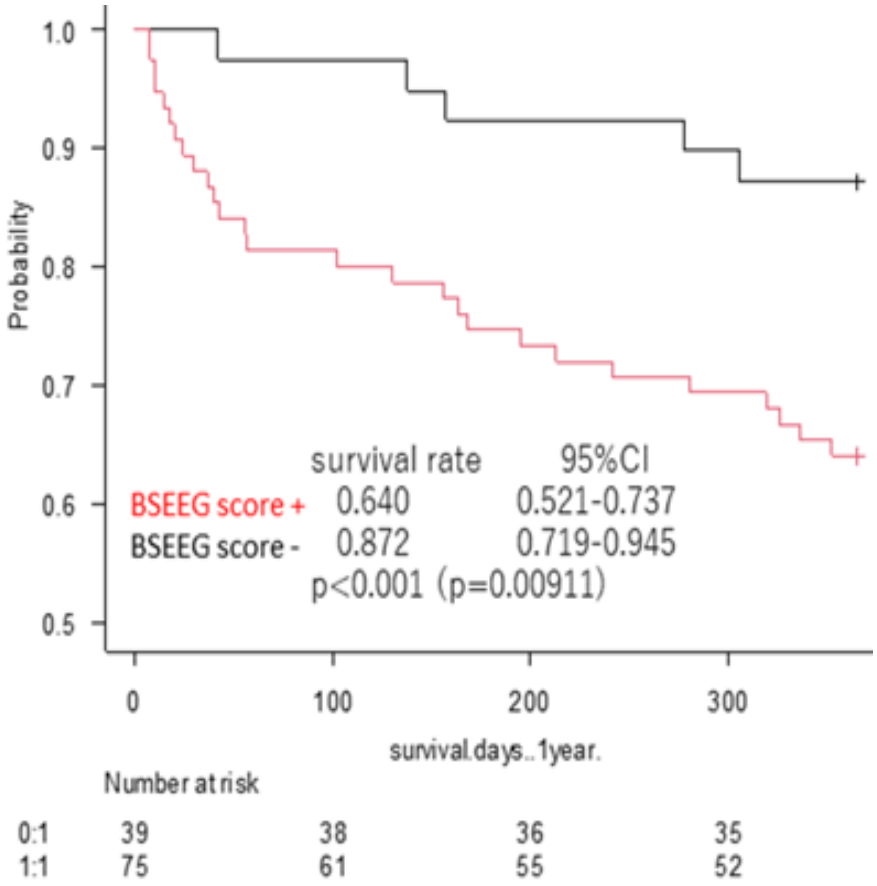
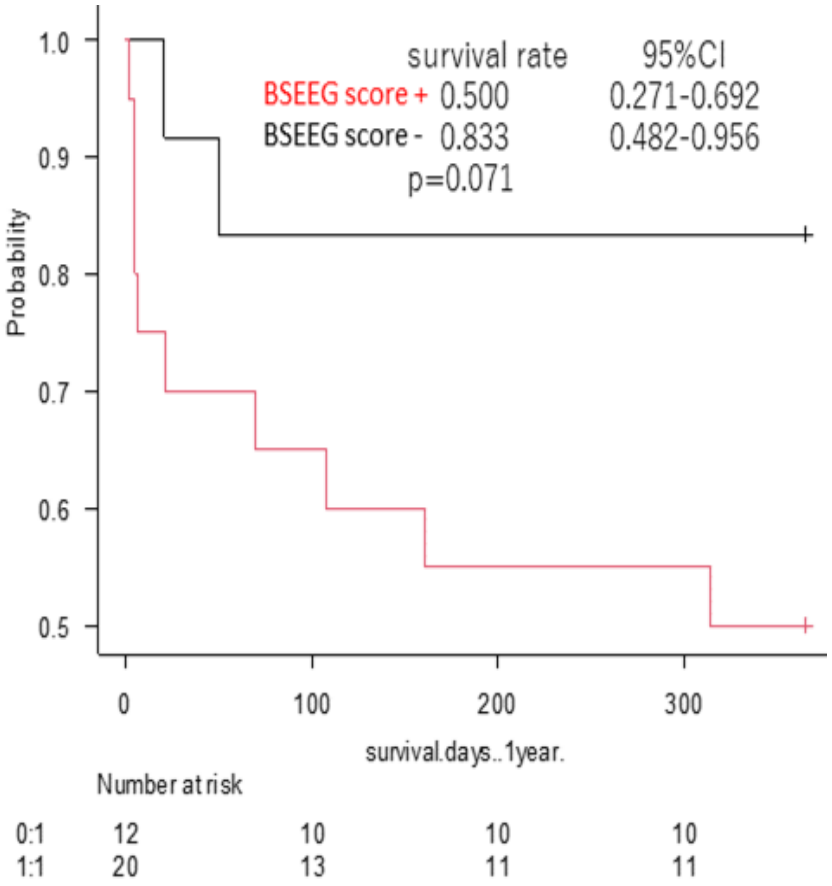
Motor subtype?

Hypo-active



Hyper-active



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Your grandma in a hospital

Question

Why do we measure blood pressure?

How about glucose?

Why not BSEEG?

Summary

- Delirium is a dangerous condition
- Early detection is vital for better outcome
- Current methods are not practical
- Simplified EEG can **detect delirium early**
- Easy to use for busy hospital settings
- This approach would **benefit patients, physicians, hospitals and health economy**.

Future directions

- I envision this BSEEG score to be used as **“next vital sign”**. Used everyday, every patient, in the hospitals, clinics, and nursing homes.

- A **thumb-size, newer device** being tested.

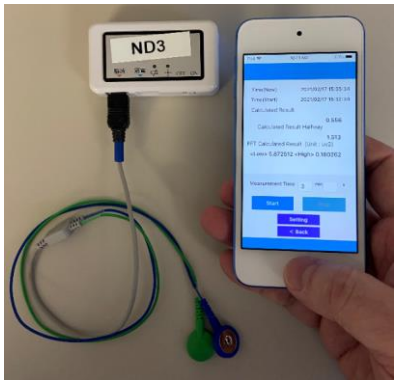
- Real goal is to **bring this technology to the patients**.

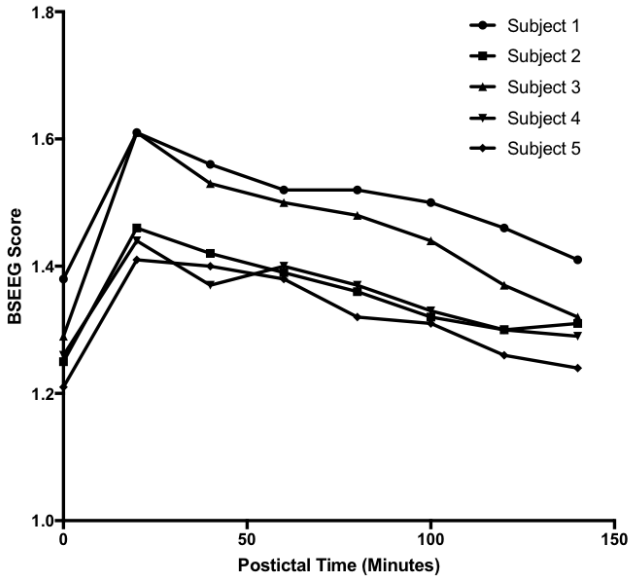
Peri-operative protocol in 2030?

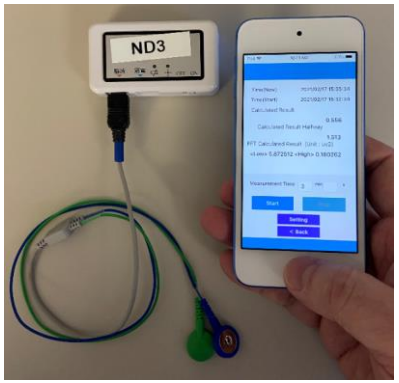
High-risk surgery:

Pre-surgery samples taken from patients:
Blood DNAm
for risk prediction
Baseline BSEEG

Post-surgery samples taken from patients:
Blood DNAm &
Post-op BSEEG
for risk monitoring







Happy Granma back home!

Funding


NIMH
National Institute
of Mental Health


NSF


Sumitomo Pharma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UIRF
University of Iowa
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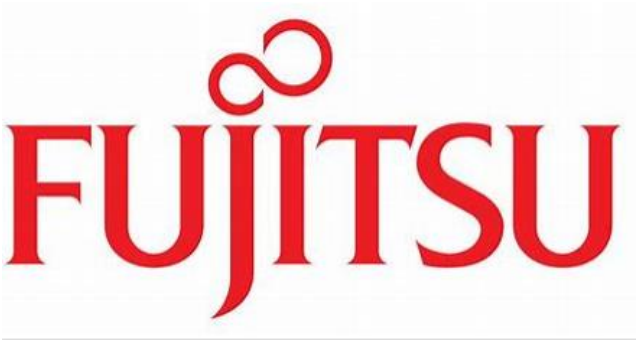
Ventures and Licensing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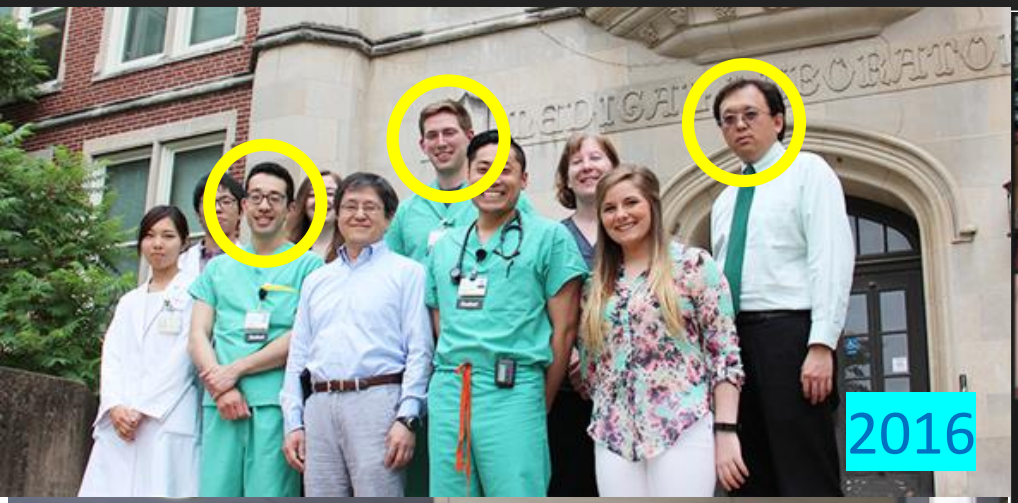

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Thank you for listening!

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