Official Title: The treatment of delirium in older adults hospitalized in internal medicine departments: an open-label pragmatic randomized-controlled trial

NCT number: NCT03398928

Date of the document: June 1, 2020

METHODS:

Trial Design: This is a pragmatic open-label randomized-controlled trial. The patients were allocated to one of two arms: acupuncture with standard-of-care (SOC) and SOC only (Fig. 1). The study protocol was reviewed and approved by the Institutional Review Board in accordance with the Helsinki Declaration (0102-14-BNZ) and registered at www.clinicaltrials.gov (NCT03398928). Trial methods and results were reported according to the Consolidated Standards of Reporting Trials (CONSORT) for non-pharmacologic interventions 2010 guidelines.[24]

Setting and participants: Trial site investigators identified consecutive eligible patients admitted to internal medicine departments at Bnai-Zion Medical Center, a 450-bed, academic hospital located in Haifa, Israel. Physicians and nurses screened daily all hospitalized patients aged 65 years and more for delirium, regardless of baseline cognitive function, using the validated 4AT delirium screening tool.[25] For patients found to have a positive 4AT screening result, investigators used the validated, four-feature-Confusion Assessment Method (CAM) tool[26] to confirm the presence of subsyndromal delirium or delirium according to DSM-5 definition. Delirium was deemed to be present when both an acute and fluctuating course and inattention and either disorganized thinking or an impaired level of consciousness was identified,[26] while subsyndromal delirium was defined as acute and fluctuating course criteria and any one of the three other criteria.[27] Participants were considered eligible for the study if they met all study criteria. Informed consent was obtained from patients or their next-of-kin as detailed in a preceding manuscript.[28] Patients were enrolled either at hospital admission (prevalent delirium) or during hospitalization (incident delirium). Patients with prevalent delirium were randomized within 48 hours of admission; patients with incident delirium were randomized within 48 hours of delirium occurrence. All patients were classified as having subsyndromal, hyperactive, hypoactive or mixed type delirium. Information was extracted from

patients, family and medical records to ensure that all study criteria are met before the patient or his/her next-of-kin was approached for consent.

Inclusion criteria:

(1) Hospitalized to an inpatient internal medicine unit.

(2) Age ≥ 65 years.

(3) Diagnosed with delirium or subsyndromal delirium within the past 48 hours.

Exclusion criteria:

(1) Having a contraindication to acupuncture (e.g., platelets ≤ 20 x 10^9/L).[29]

(2) History of severe dementia (documented history and/or IQCODE score ≥ 4).

(3) Acute neurological injury (stroke).

(4) History of schizophrenia or a formal thought disorder.

(5) Active acute alcohol or drug withdrawal.

(6) History of end stage liver failure.

(7) Communication barriers preventing delirium assessment.

Interventions: Enrolled patients were allocated to one of the following treatment groups:

1. Acupuncture with SOC (acupuncture group): up to 5 sessions of acupuncture in a 1-week period or until discharge, and SOC treatment for up to 1 week or until discharge.

2. SOC only (SOC or control group): up to 1 week or until discharge.

The development of the intervention protocol was inspired from the 2008 Medical Research Council guideline for developing complex interventions, as described in a previous manuscript.[28] Acupuncture treatment was reported according to STRICTA guidelines[30] in http://www.stricta.info.

Acupuncture rationale: The acupuncture was performed in a Traditional Chinese Medicine (TCM) style. Patients were categorized according to TCM syndromes of hyperactive delirium (Fire blazing and Phlegm fire); hypoactive delirium (Qi deficiency, Yang deficiency, Yang deficiency with Phlegm, and Qi obstructed), or mixed delirium (Blood and Qi deficiency, and

Yin deficiency). The TCM categorization was based on pulse diagnosis and clinical observation. Due to the difficulty of tongue examination and anamnesis in delirious patients, these elements were rarely used in the diagnostic process.[31] Then, TCM-based acupuncture treatment was performed according to the delirium TCM syndrome category.[31]

Details of needling: During the treatment, the acupuncturists used 75% alcohol pads to sterilize the skin around the acupoints. Subsequently, sterile disposable needles were inserted in the acupoints. An average of five Seirin FDA-approved needles of 5-cm length and 0.2-mm diameter were inserted. The puncture depth varied with anatomical location from 0.5 to 1 cm. Manual needle stimulation was performed and *de qi* sensation (e.g. dullness, sourness, heaviness, tingling sensation around the needle) was not sought.

Treatment regimen: The number of acupuncture treatments was set at up to five treatments in the one-week study period (treatments was not provided on weekends) or until the patient is delirium-free for 48 hours. Each session lasted 15-20 minutes.

Other components of treatment: Patients of acupuncture group also received SOC. Prior to the start of the study, a multicomponent protocol for delirium management was developed and implemented in internal medicine departments. This protocol was based on best literature evidence, current practice guidelines[32,33] and the opinions of geriatric and psychiatric consultants, and included both pharmacological and non-pharmacologic interventions as published in a preceding manuscript.[28] All clinicians working in the internal medicine departments were educated regarding the protocol and its use. This protocol was defined "SOC" for the study. Since the actual care of patients may differ according to clinical data and physician consideration, the use of psychotropic drugs (including antipsychotics) during hospitalization were documented and compared between the study arms. No other complementary medicine therapies other than acupuncture were added. Explanations were given to patients and their next-of-kin on potential benefits and side effects of acupuncture and treatment was administered only after they signed informed consent.

Practitioner background: The treatment was administered by seven acupuncturists with at least 5 years of clinical experience in a hospital setting.

Control intervention: In the control group, patients received SOC only.

Outcomes: All daily outcomes were collected daily for one week after randomization or until the patient was discharged from the hospital.

Primary outcome: Our primary endpoint was resolution of delirium during the 7 days of evaluation and was measured as time-to-first remission of delirium and number of delirium-free days, based on daily assessment of CAM scale.

Secondary outcomes:

1. Delirium severity: Comparison of the sum of long CAM-severity (CAM-S) score[34] from day 2 (before treatment in the second day of the study) until day 7 (last day of evaluation). The CAM-S tool includes 10 delirium-related items, the first one being rated on a 0-1 scale and the nine followings in a 0-2 scale for a total score ranging from 0-19. The items include the four CAM items described earlier in addition to disorientation, memory impairment, perceptual disturbances, psychomotor agitation, psychomotor retardation and altered sleep-wake cycle. The sum of long CAM-S score has been shown to best reflect both 30-day and 90-day post-hospital outcomes in patients with delirium.[34]

2. Number of days an antipsychotic drug was administered: as mentioned in the daily study investigator chart review.

3. Pain: based on twice daily Visual Analogue Scale (VAS) scores for communicating patients and FRAAC (Facial expression, Respiration, Activity, Audibility, Cry and consolability) scores for non-communicating patients. Both scales are rated on a 0-10 score and are comparable in terms of pain severity. They were routinely recorded twice daily by registered nurses.

4. Sleep quality: as assessed by the tenth CAM-S item.

5. Delirium complications: daily evaluation of falls, pulling-out intravenous or urinary catheters, new or increase in pressure ulcers grade.

6. Length of hospital stay

7. Functional status at discharge: based on Katz ADL at discharge as evaluated by study investigators.

8. Safety and adverse events: A checklist with acupuncture adverse events based on the AcupAE questionnaire[35] was adapted to our study. All adverse events were recorded and monitored daily. Acupuncture-associated adverse events were discussed by the research team and the family of patients and addressed accordingly. Severe adverse events requiring patient exclusion

from the clinical trial included pneumothorax, massive bleeding, or infection in the acupoint area requiring systemic antibiotic treatment.

Sample size calculation: Since no previous study has evaluated an acupuncture-based intervention in older adults with delirium, a pilot study of 32 patients [acupuncture group (n=24); control group (n=8)] was designed to estimate accurately the sample size for our current study. In the pilot study, delirium-free days were 3.2±1.6 in the acupuncture group as compared with 1.7±2.4 in the control group. Taking into account a Type I error (alpha) of 0.05, a power of 0.80, pairwise comparison between our two study arms, and using G*Power 3.1.9.4 software, we calculated a minimal sample size of 28 patients in each of the 2 study arms.

Randomization: Patients were randomized in two groups by convenience allocation according to acupuncturists' working days: patients with delirium diagnosed on Sunday, Monday, Wednesday or Thursday were assigned to the acupuncture arm, while patients with delirium diagnosed on Tuesday, Friday or Saturday were assigned to SOC arm. Blinding was clearly not feasible.

Statistical methods: Demographic and clinical data was analyzed at baseline to measure the balance among the study groups. Quantitative variables were described using mean and standard deviation or median with range (minimum and maximum) depending on their distribution. Qualitative variables were described using frequency and percentage distributions. Next, we showed that our variables distribute equally between the two groups. For comparing normally distributed variables between our study groups, we used the t-test for independent samples. For comparing variables that do not distribute normally between our study groups, we used the Mann-Whitney test. For comparing qualitative variables between our study groups, we used the independent Chi-square test and Fisher exact test. Time-to-first delirium remission was evaluated using the Kaplan-Meier product limit survival estimator with log-rank between-group comparison and Cox regression was performed for multivariate adjustment of potential confounders. Hazard ratio (HR) with confidence intervals (CI) was calculated for each independent variable and controlled for all other independent variables in the regression. Patients who died or were discharged before day 7 had all subsequent days counted as the last day of evaluation in terms of both CAM and CAM-S. Intention-to-treat (ITT) analysis was planned to provide more information on the effect of the intervention. We explored the variables for possible collinearities, interaction, and confounders. All comparisons were two-sided with

significance level set at $p<0.05$. Data analysis was performed using IBM SPSS version 22 statistics software.

RESULTS:

Baseline patient data: Overall, 132 patients were screened for eligibility. Among them, 81 were recruited – 50 to the acupuncture arm and 31 to the SOC arm. Baseline sociodemographic and medical characteristics were similar in the two study arms as shown in Table 1. To note, all the patients randomized to the acupuncture arm were treated with acupuncture, while no patient assigned to the SOC arm received acupuncture (Fig. 1), so the planned ITT analysis was not required. In the acupuncture arm, 14 (28%) were censored (dead/discharged in the 7 days of follow-up), as compared with 8 (26%) in the SOC arm (p=0.87). No difference in the baseline characteristics was noted between censored patients and patients completing the 7 days of follow-up.

Primary endpoint: Time-to-first delirium remission was shorter in the acupuncture arm as compared to the SOC arm (p<0.001 for log-rank comparison, Fig. 2A). In the 7 days of evaluation, we calculated a number needed to treat (NNT) of 3 for first delirium remission. A multivariate Cox regression analysis was also conducted to evaluate the association of study arm allocation with the primary outcome (time-to-first delirium remission), adjusted for potential sociodemographic and medical confounders (age, gender, APACHE-II score, Charlson comorbidity index, number of psychotropic drugs, mobilization, cognitive impairment, reason for admission and type of delirium). The analysis showed that after adjusting for potential confounders, the time-to-first remission of delirium in the acupuncture arm was significantly shorter than in the SOC arm [HR 0.267 (95% CI 0.098-0.726, p=0.010), Fig. 2B], while HR of potential confounders were not statistically significant. This means that acupuncture associated with SOC significantly increased the incidence of delirium remission by about 4-times, as compared to SOC only, after adjusting for sociodemographic and medical characteristics (model significance: p=0.042). Furthermore, in the 7 days of evaluation, a significantly higher number of delirium-free days was found in the acupuncture arm [median 5.5 (0-6)] as compared with the SOC arm [median 0 (0-6)], p<0.001. Based on these results, the power of the study was calculated as 100%.

Secondary endpoints:

Delirium severity: The long CAM-S sum from day 2 to day 7 of evaluation was significantly lower in the acupuncture group [11 (24%) with no delirium, 6 (13%) with low severity, 9 (20%) with moderate severity and 19 (42%) with high severity] as compared with the control group

[3 (11%) with no delirium, 0 with low severity, 1 (4%) with moderate severity and 24 (86%) with high severity], p=0.002, Fig. 3.

Number of psychotropic drugs-free days: The number of psychotropic drugs-free days in the 7 days of evaluation was similar in the two study groups [median: 7 (0-7) in acupuncture arm vs 7 (0-7) in SOC arm, p=0.253].

Pain: No difference in daily evaluation of pain intensity was found between the two study arms in the 7 days of evaluation.

Sleep: According to the tenth CAM-S item daily evaluation, no difference was found in terms of quality of sleep between the study arms during the 7 days of evaluation.

Delirium complications: No difference was found in terms of delirium-related complications between the study arms [median: 0 (0-6) complications in acupuncture arm vs 0 (0-1) complications in SOC arm, p=0.665].

Length of hospitalization: The duration of hospitalization was similar in the 2 study arms [median: 13 (2-67) days in the acupuncture arm vs 12 (2-54) in the SOC arm, p=0.945].

Functional status at discharge: Katz ADL at discharge was similar in the two study arms [median: 2 (0-6) in the acupuncture arm vs 3.5 (0-6) in the SOC arm, p=0.945].

Safety: No safety event was reported according to daily AcupAE evaluation.

Tables and figures:

Table 1: Baseline characteristics

Baseline characteristics		Acupuncture + SOC (n=50)	SOC only (n=31)	p
Male gender – N (%)		25 (50%)	19 (61%)	0.36
Age (years) – Mean (SD)		84.0 (7.8)	85.3 (6.7)	0.45
Prevalent delirium – N (%)		26 (52%)	16 (52%)	1.00
APACHE-II – Median (min-max)		9 (5-22)	11 (6-19)	0.31
Number of medications – Median (min-max)		8 (0-16)	9 (1-15)	0.38
Number of psychotropic drugs – Median (min-max)		1 (0-5)	1 (0-3)	0.66
Mobilization – N (%)	Normal	24 (48%)	9 (19%)	0.19
	Walking aid	15 (30%)	15 (48%)	
	Wheelchair	2 (4%)	3 (10%)	
	Bedridden	9 (18%)	4 (13%)	
IQCODE – N (%)	Normal cognitive status	28 (56%)	12 (39%)	0.35
	Mild dementia	17 (34%)	16 (52%)	
	Moderate dementia	4 (8%)	3 (10%)	
	Severe dementia	1 (2%)	0	
ADL – Median (min-max)		4.5 (0-6)	4 (0-6)	0.36
Reason for admission – N (%)	Infection	19 (38%)	12 (39%)	0.94
	Dyspnea	9 (18%)	9 (29%)	
	General Deterioration	8 (16%)	4 (13%)	
	Falls	3 (6%)	3 (10%)	
	Anemia	2 (4%)	1 (3%)	
	Other	9 (18%)	2 (6%)	
Delirium category – N (%)	Hyperactive	23 (46%)	12 (39%)	0.45
	Hypoactive	15 (30%)	12 (39%)	
	Mixed	9 (18%)	3 (10%)	
	Subsyndromal	3 (6%)	4 (13%)	
Hearing and/or visual impairment – N (%)		26 (52%)	22 (71%)	0.11
Charlson Comorbidity Index – Median (min-max)		7 (4-13)	7 (4-11)	0.97
Baseline delirium severity (Long CAM-S) – Median (min-max)		8 (3-15)	9 (4-14)	0.63

Legend: ADL: Activities of Daily Living; APACHE: Acute Physiology And Chronic Health Evaluation; CAM-S: Confusion Assessment Method Severity; SOC: Standard-of-care.

Figure 1: CONSORT Flow Diagram for non-pharmacologic interventions

Legend: SOC: Standard-of-care

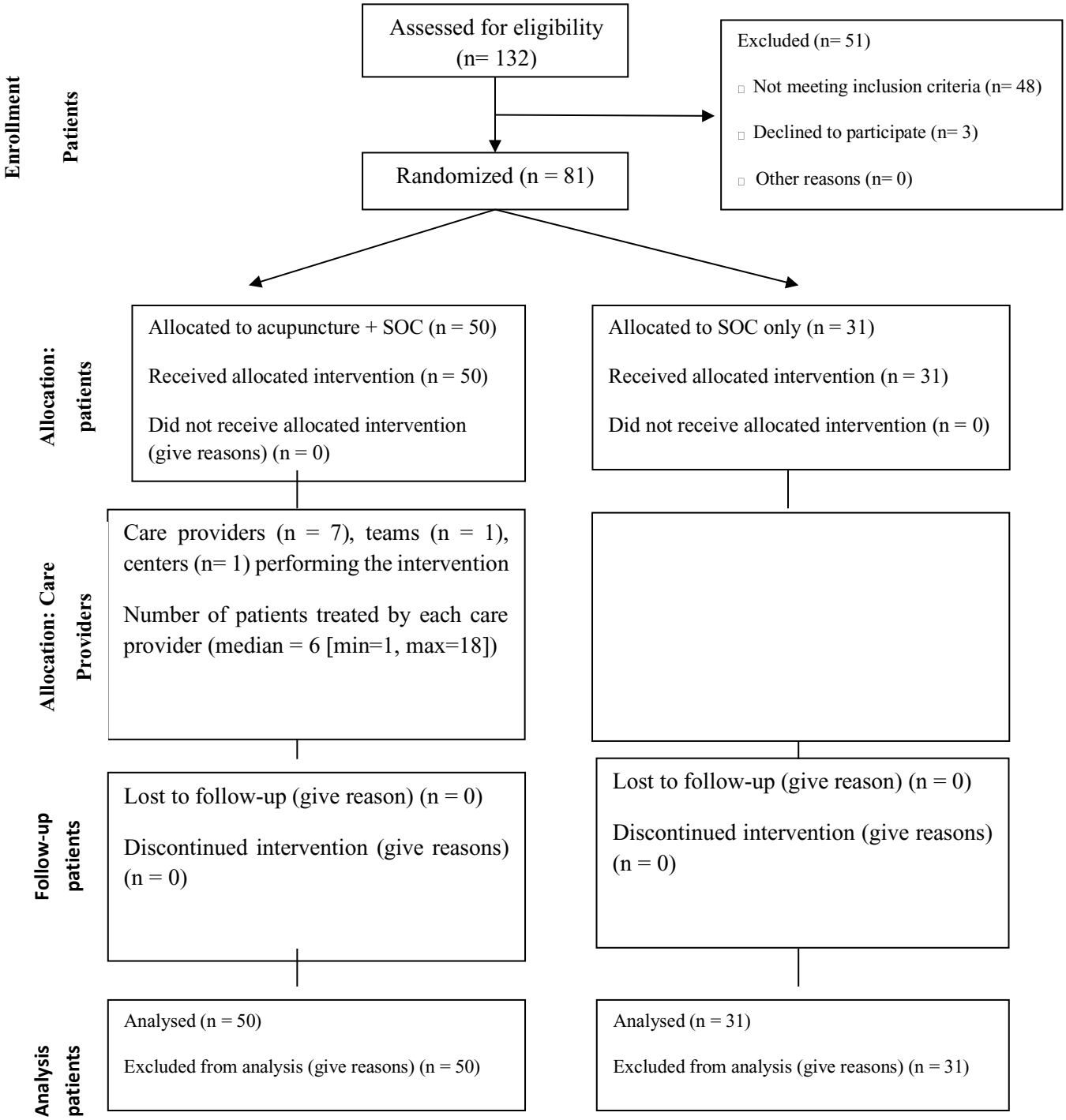
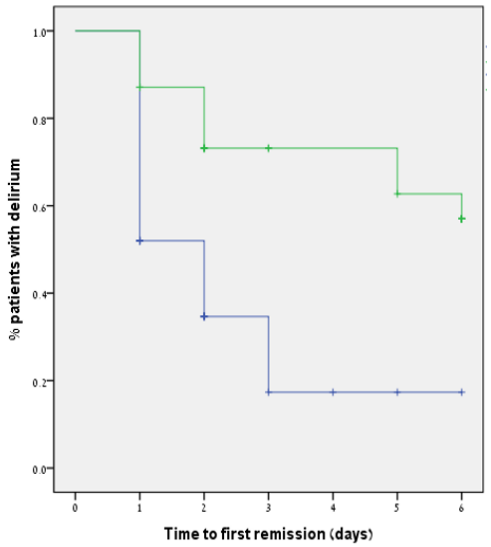
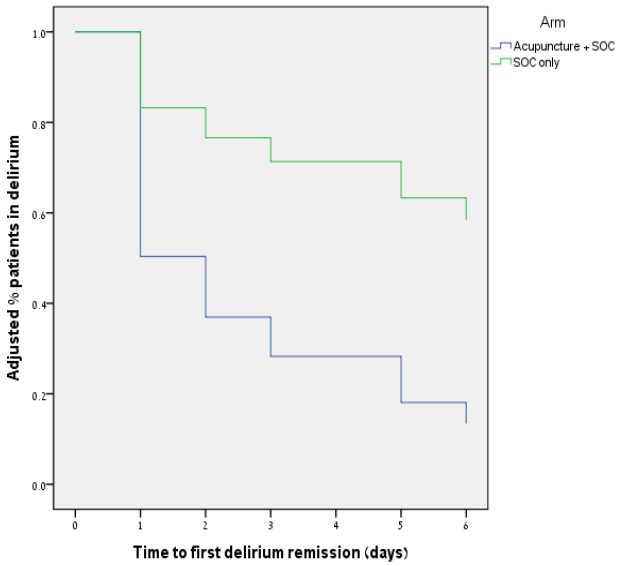


Figure 2: Time to first delirium remission





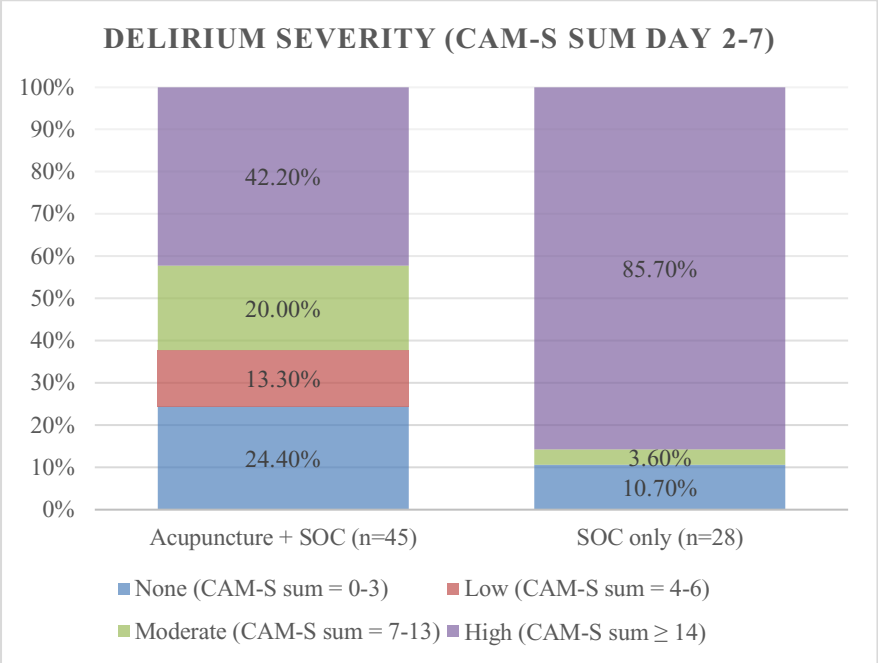
A. p<0.001

B. HR 0.267 (95% CI: 0.098-0.726, p=0.010)

A. Kaplan-Meier graph with Log-rank comparison of time to first delirium remission between study groups. **B.** Cox regression analysis of time to first delirium remission considering sociodemographic and medical covariates.

Legend: SOC: Standard-of-care.

Figure 3: Delirium severity



Legend: CAM-S: Confusion Assessment Method Severity; SOC: Standard-of-care.