Association of Low Dose Ketamine with Hallucinations in Critically Ill Patients: A Target Trial Emulation

ONLINE SUPPLEMENT

ADDITIONAL STATISTICAL ANALYSIS

Missing baseline data from the first 24 hours after ICU admission was imputed using multiple imputation by chained equations. The list of predictors included the outcome variable, the failure time, and baseline covariates. In case of missing covariate values during the follow-up, the last observed value of a covariate was carried forward, reflecting the clinical practice at bedside.

Subgroup analyses were performed according to age (< 50 vs. 50 – 65 vs. ≥ 65 years), type of admission (medical vs. surgical), use of mechanical ventilation (yes vs. no) and severity of illness (APACHE III < 48 vs. ≥ 48). The following sensitivity analyses were performed: 1) complete case analysis (not imputing missing values); 2) additional analysis including the daily use of antipsychotics (haloperidol, quetiapine, risperidone and/or olanzapine) and/or benzodiazepines as daily confounders (analysis performed in a restricted cohort of patients where information about these medications was available); 3) additional analysis including the daily level of sedation (assessed by RASS) as time-dependent confounder; 4) additional analysis restricting the dataset to patient-days with RASS between -1 and 1, representing days when hallucinations could be reliably assessed; 5) additional analysis adjusted for a binary indicator of assessable days (RASS -1 to 1); and 6) assessment of the impact of the use of low dose ketamine on hallucination using parametric g-formula (as described below). The g-formula was used to confirm the findings from the main model and to assess the impact of different timing and duration of the intervention.

METHODS MARGINAL STRUCTURAL MODELS

Dataset

The dataset for the analyses was transformed to a long dataset with each patient-day as a separate record (or row). All observations start at day 0 and goes until development of the first episode of hallucination, ICU discharge, death or day 30, whichever comes first. Thus, patients can have from 1 to 31 observations (or rows). All records are sorted by a unique identification number and, within each patient, by day of follow-up.

Step 1. Probability of remaining off ketamine

First, two pooled logistic regression models were fitted for the probability of remaining off ketamine. The outcome variable in these models was a variable indicating whether the patient had started or remained off ketamine in that day. Analyses were restricted to patients not previously on ketamine by specifying that either day of follow-up is less than or equal to day of onset of ketamine or ketamine was never initiated during the follow-up period.

The first model included a time-dependent intercept and the baseline covariates as described in the main paper. The second model included, in addition, the time-dependent covariates of delirium, use of dexmedetomidine and NLP-Dx-BD. The time-dependent intercept was estimated by a smooth function of the day since beginning of follow-up using natural cubic splines with five knots.

Step 2. Probability of remaining free of competing event

Second, two pooled logistic regression models were fitted for the probability of remaining free of competing event. The outcome variable in these models was a

variable indicating whether the patient had a competing event or not in that day. The first model included the time-dependent intercept and the baseline covariates, and the second model included, in addition, the time-dependent covariates. Both models included the use of ketamine.

Step 3. Calculate of weights

The weights for each patient-day were calculated from the predicted values of the previous four models ('pketamine$_0$', 'pketamine$_w$', 'pnocomprisk$_0$' and 'pnocomprisk$_w$'). These four weights were merged into one dataset and the numerator 'k2$_0$' and the denominator 'k2$_w$' were calculated as described below.

$$k2_0 = 1 * pnocomprisk_0$$

$$k2_w = 1 * pnocomprisk_w$$

In addition, the numerator 'k1$_0$' and the denominator 'k1$_w$' were calculated for days which the patient has not yet started ketamine from the first two models as below.

$$k1_0 = 1 * p\text{ketamine}_0$$

$$k1_w = 1 * p\text{ketamine}_\text{w}$$

For a day in which a patient did begin ketamine, the weight was multiplied by 1 minus the predicted value as described below.

$$k1_0 = k1_0 * (1 - pketamine_0)$$

$$k1_w = k1_w * (1 - pketamine_w)$$

For days subsequent to starting ketamine, the weights were no longer updated. Then, the numerators and denominators were used to calculate stabilised weights, and the denominators alone to calculate nonstabilised weights, as described below:

$$Stabilized\ weights = \frac{(k1_0 * k2_0)}{(k1_w * k2_w)}$$

$$Nonstabilized\ weights = \frac{1}{(k1_w * k2_w)}$$

Step 4. Final model

A final weighted pooled logistic regression model using generalized estimating equations was fitted to estimate the causal parameter and its robust standard error. The outcome variable of this model was a dichotomous variable indicating whether the patient had hallucination or not in that day. The patient identification variable was included to calculate robust standard errors, and an independent working correlation matrix was specified. The model was fitted using stabilised weights.

METHODS G-FORMULA

Parametric regression models were fitted to estimate the complete joint distribution of the outcome and time-dependent covariates given previous treatment and covariate history. This joint distribution was then used in Monte Carlo simulations to estimate the risk of the outcome if all patients were always treated with low dose ketamine (‘always treated’) or if all patients never received low dose ketamine (‘never treated’), and to compare it with the observed risk under natural course (usual care). Non-parametric bootstrapping with 500 resamples was used to estimate 95% confidence intervals (CIs).

G-formula was implemented following three steps: 1) parametric regression models for each of the time-dependent variables as a function of prior risk factor history at each time point; 2) simulation of the course in the ICU for a large pseudopopulation of patients under the treatment strategy of interest; and 3) bootstrap to obtain 95% CI for the estimated risks of outcomes effect estimates between interventions. All models were adjusted by the same set of baseline covariates and time-dependent covariates as in the marginal structural model.

In additional analyses, the impact of timing of initiation and duration of treatment on outcome were assessed. More specifically, the causal effect on hallucination for the following strategies compared with natural course were assessed: early start (day 1 to 5), delayed start (day 5 to 10), late start (day 10 to 15), early start and short duration (day 1 to 2), early start and middle duration (day 1 to 3), early start and long duration (day 1 to 4), late start and short duration (day 10 to 11), late start and middle duration (day 10 to 12), late start and long duration (day 10 to 13).

eTable 1 – Summary of the Protocol of the Target Trial Assessing the Impact of Low Dose Ketamine on Hallucinations

Components	Hypothetical randomised trial	Emulation
Eligibility	All adult patients admitted to the ICUs of the Austin Hospital, Melbourne between June 2016 and April 2021. Patients who developed hallucination before the first dose of ketamine and patients with missing data in ICU length of stay, time until ketamine use or in time until hallucination were excluded	Same as hypothetical trial
Treatment strategies	• Received analgesia with low dose ketamine • Did not receive low dose ketamine	Same as hypothetical trial
Treatment assignment	Patients are randomly assigned to one of the strategies. Stratification was performed based on clinical characteristics. The treatment team was aware of the assigned strategy	We assumed that patients were randomly assigned within levels of the following baseline variables: age, sex, type of admission (medical or surgical), planned or unplanned admission, the Australian and New Zealand Risk of Death (ANZROD) after log transformation, admission after medical emergency team call, cardiac arrest in the first 24 hours, acute kidney injury at ICU admission, admission diagnosis, ICU source of admission, chronic cardiovascular disease, hepatic failure, metastatic cancer, leukemia, use of renal replacement therapy, use of vasopressor/inotropes and use of mechanical ventilation
Follow-up	The follow-up started at the time of assignment to a strategy and ended at either at: • First episode of hallucinations • Discharge from ICU (competing event) • Death (competing event) • 30 days of follow-up in ICU whichever comes first	Same as hypothetical trial
Primary outcomes	30-day hallucination	Same as hypothetical trial
Causal contrast	Per protocol effect	Observational analogue of the per protocol effect
Statistical analysis	In the per-protocol analysis, patients were censored when they deviated from their assigned strategy. The per-protocol effect was estimated after adjustment for baseline variables and for time-dependent variables associated with adherence to a strategy considering analgesia with low ketamine	Same as hypothetical trial. The per-protocol effect was estimated using a methodological approach based on marginal structural models with inverse probability weighting. The per-protocol effect under full adherence was also estimated using the parametric g-formula. The value of each density function for all possible covariate histories was estimated under parametric modelling assumptions. The approximated sum over all histories was subsequently calculated via Monte Carlo simulation.

eTable 2 – Rate of Missing Data

	Overall (*n* = 7514)	Low Dose Ketamine (*n* = 625)	No Ketamine (*n* = 6889)
Age	0 (0.0)	0 (0.0)	0 (0.0)
Male gender	6 (0.1)	0 (0.0)	6 (0.1)
Weight	6044 (80.4)	469 (75.0)	5575 (80.9)
Body mass index	6557 (87.3)	508 (81.3)	6049 (87.8)
Weight	5494 (73.1)	414 (66.2)	5080 (73.7)
APACHE III	7 (0.1)	0 (0.0)	7 (0.1)
ANZROD	47 (0.6)	1 (0.2)	46 (0.7)
Type of admission	3 (0.0)	0 (0.0)	3 (0.0)
Planned admission	0 (0.0)	0 (0.0)	0 (0.0)
MET call admission	1 (0.0)	0 (0.0)	1 (0.0)
Cardiac arrest	11 (0.1)	0 (0.0)	11 (0.2)
Acute renal failure	53 (0.7)	4 (0.6)	49 (0.7)
Admission diagnosis	3 (0.0)	0 (0.0)	3 (0.0)
ICU source of admission	0 (0.0)	0 (0.0)	0 (0.0)
Co-existing disorders			
Diabetes	6171 (82.1)	513 (82.1)	5658 (82.1)
Chronic lung disease	0 (0.0)	0 (0.0)	0 (0.0)
Chronic cardiovascular disease	0 (0.0)	0 (0.0)	0 (0.0)
Cirrhosis	0 (0.0)	0 (0.0)	0 (0.0)
Chronic kidney disease	0 (0.0)	0 (0.0)	0 (0.0)
Chronic immune disease	0 (0.0)	0 (0.0)	0 (0.0)
Immunosuppression	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic failure	0 (0.0)	0 (0.0)	0 (0.0)
Lymphoma	0 (0.0)	0 (0.0)	0 (0.0)
Metastatic cancer	0 (0.0)	0 (0.0)	0 (0.0)
Leukemia	0 (0.0)	0 (0.0)	0 (0.0)
Organ support			
ECMO	2331 (31.0)	166 (26.6)	2165 (31.4)
Vasopressor or inotropes	2329 (31.0)	166 (26.6)	2163 (31.4)
Invasive ventilation	1190 (15.8)	88 (14.1)	1102 (16.0)
Non-invasive ventilation	2300 (30.6)	163 (26.1)	2137 (31.0)
Renal replacement therapy	2193 (29.2)	161 (25.8)	2032 (29.5)
Laboratory tests			
pH	1098 (14.6)	46 (7.4)	1052 (15.3)
PaO_2 / FiO_2	1097 (14.6)	46 (7.4)	1051 (15.3)
$PaCO_2$	1110 (14.8)	47 (7.5)	1063 (15.4)
Lactate	2645 (35.2)	174 (27.8)	2471 (35.9)
Highest creatinine	1163 (15.5)	99 (15.8)	1064 (15.4)
Lowest platelet	1155 (15.4)	100 (16.0)	1055 (15.3)
Vital signs			
Lowest MAP	128 (1.7)	14 (2.2)	114 (1.7)
Highest RR	104 (1.4)	9 (1.4)	95 (1.4)

eTable 2 – Rate of Missing Data

	Overall (*n* = 7514)	Low Dose Ketamine (*n* = 625)	No Ketamine (*n* = 6889)
Highest temperature	90 (1.2)	10 (1.6)	80 (1.2)
Urine output	2488 (33.1)	174 (27.8)	2314 (33.6)
Primary outcome			
Hallucination within 30 days	0 (0.0)	0 (0.0)	0 (0.0)
Secondary neurological outcomes			
Delirium within 30 days	8 (0.1)	1 (0.2)	7 (0.1)
NLP-Dx-BD	8 (0.1)	1 (0.2)	7 (0.1)
Hyperactive	8 (0.1)	1 (0.2)	7 (0.1)
Hypoactive	8 (0.1)	1 (0.2)	7 (0.1)
Mixed	8 (0.1)	1 (0.2)	7 (0.1)
Clinical outcomes			
Duration of ventilation	1204 (30.9)	88 (25.4)	1116 (31.4)
ICU length of stay	1 (0.0)	0 (0.0)	1 (0.0)
Hospital length of stay	6 (0.1)	1 (0.2)	5 (0.1)
30-day ICU mortality	3 (0.0)	0 (0.0)	3 (0.0)

eTable 3 – Characteristics of Ketamine Use and Hallucination Assessment in the Included Patients

	Overall (*n* = 7514)	Low Dose Ketamine (*n* = 625)	No Ketamine (*n* = 6889)
Characteristics of ketamine use			
Days until ketamine start	0.0 (0.0 - 1.0)	0.0 (0.0 - 1.0)	---
Total dose of ketamine, mg	208 (104 - 438)	208 (104 - 438)	---
Mean daily dose of ketamine, mg/h	8.5 (6.3 - 11.6)	8.5 (6.3 - 11.6)	---
mg/kg/h	0.11 (0.08 - 0.16) (*n* = 211)	0.11 (0.08 - 0.16) (*n* = 211)	---
Duration of ketamine use, days	1.2 (0.6 - 2.2)	1.2 (0.6 - 2.2)	---
Characteristics of hallucination assessment			
Total number of notes assessed	11 (5 - 22)	15 (7 - 28)	10 (5 - 21)
Number of episodes of hallucination	0 (0 - 0)	0 (0 - 1)	0 (0 - 0)
Percentage of notes with hallucination	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.8)	0.0 (0.0 - 0.0)
Percentage of days when hallucination could be assessed*			
Light sedation (RASS -2 to 1)	87.5 (50.0 - 100.0) (*n* = 945)	100.0 (62.0 - 100.0) (*n* = 111)	83.3 (50.0 - 100.0) (*n* = 834)
Awake (RASS ≥ -2)	100.0 (90.0 - 100.0) (*n* = 945)	100.0 (100.0 - 100.0) (*n* = 111)	100.0 (88.1 - 100.0) (*n* = 834)

Data are median (IQR) or N (%).

* Assessed in patients not receiving mechanical ventilation.

eTable 4 – Full Multivariable Model of the Association of Use of Low Dose Ketamine and Hallucination Within 30 Days

	Odds Ratio (95% CI)	*p* value
Intercept	0.00 (0.00 to 0.01)	< 0.001
Use of low dose ketamine	6.46 (5.17 to 8.07)	< 0.001
Age	1.00 (0.99 to 1.01)	0.261
Sex		
Female	1 (Reference)	
Indeterminant	Not estimated	---
Male	1.07 (0.90 to 1.27)	0.420
ANZROD	0.98 (0.90 to 1.06)	0.554
Type of admission		
Medical	1 (Reference)	
Surgical	0.59 (0.30 to 1.17)	0.131
Planned admission	0.84 (0.66 to 1.07)	0.165
MET call admission	2.09 (1.23 to 3.53)	0.006
Cardiac arrest	0.77 (0.44 to 1.37)	0.379
Acute renal failure	1.63 (1.15 to 2.32)	0.007
Admission diagnosis		
Cardiovascular	1 (Reference)	
Gastrointestinal	1.71 (1.33 to 2.19)	< 0.001
Gynecological	1.50 (0.16 to 13.92)	0.724
Hematological	2.29 (0.92 to 5.66)	0.073
Metabolic	2.39 (1.57 to 3.63)	< 0.001
Musculoskeletal	1.99 (1.17 to 3.40)	0.012
Musculoskeletal/Skin	2.64 (0.34 to 20.84)	0.356
Neurological	1.20 (0.84 to 1.70)	0.319
Renal/Genitourinary	1.05 (0.63 to 1.75)	0.860
Respiratory	1.05 (0.76 to 1.46)	0.756
Sepsis	1.36 (0.94 to 1.96)	0.101
Trauma	1.36 (0.87 to 2.12)	0.180
ICU source of admission		
Emergency department	1 (Reference)	
ICU other hospital	0.84 (0.52 to 1.36)	0.479
ICU same hospital	0.91 (0.08 to 10.18)	0.942
Operating room	1.67 (0.83 to 3.38)	0.151
Other	0.00 (0.00 to 0.00)	< 0.001
Other hospital	0.89 (0.63 to 1.27)	0.524
Ward	0.54 (0.30 to 0.97)	0.039
Co-existing disorders		
Chronic cardiovascular disease	1.51 (1.05 to 2.18)	0.026
Hepatic failure	1.06 (0.60 to 1.88)	0.839
Metastatic cancer	1.20 (0.79 to 1.81)	0.398
Leukemia	1.00 (0.53 to 1.88)	0.993

Organ support		
Renal replacement therapy	0.95 (0.73 to 1.24)	0.710
Vasopressor or inotropes	0.88 (0.68 to 1.15)	0.365
Invasive ventilation	1.33 (0.99 to 1.77)	0.051
Day		
1 knot	1 (Reference)	
2 knot	2.70 (1.80 to 4.06)	< 0.001
3 knot	0.00 (0.00 to 0.00)	0.001
4 knot	Not estimated	0.002
5 knot	0.00 (0.00 to 0.00)	0.008

Abbreviations: ANZROD is Australian and New Zealand Risk of Death; MET is medical emergency team; ICU is intensive care unit.

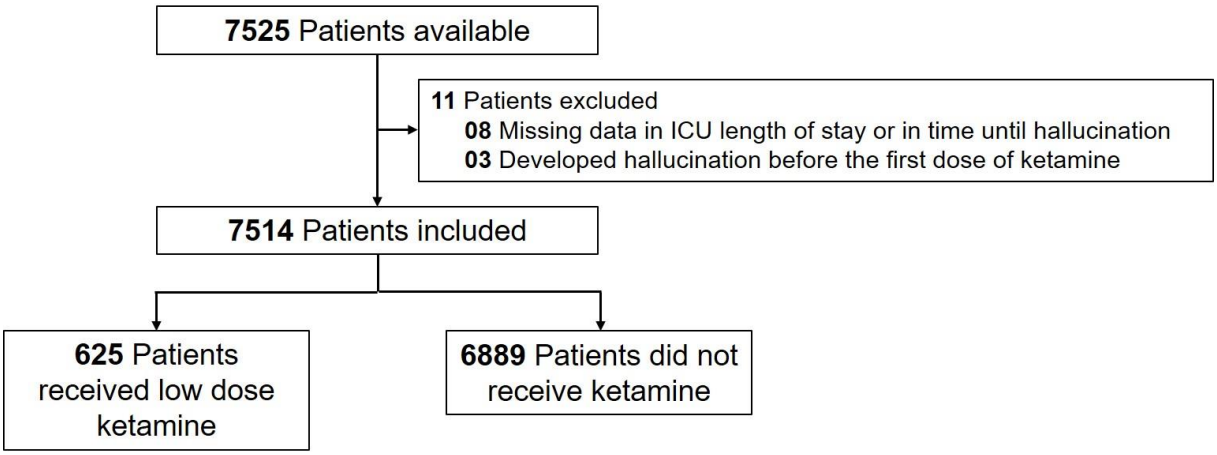
All models adjusted for age, sex, type of admission (medical or surgical), planned or unplanned admission, the Australian and New Zealand Risk of Death (ANZROD) after log transformation, admission after medical emergency team call, cardiac arrest in the first 24 hours, acute kidney injury at ICU admission, admission diagnosis, ICU source of admission, chronic cardiovascular disease, hepatic failure, metastatic cancer, leukemia, use of renal replacement therapy, use of vasopressor/inotropes and use of mechanical ventilation. The following time-dependent variables were included: delirium, use of dexmedetomidine and NLP-Dx-BD. All models included the day, and the time-dependent intercept was estimated by a smooth function of the day since beginning of follow-up using natural cubic splines with five knots.

eTable 5 – Additional Results of the G-Formula Analysis

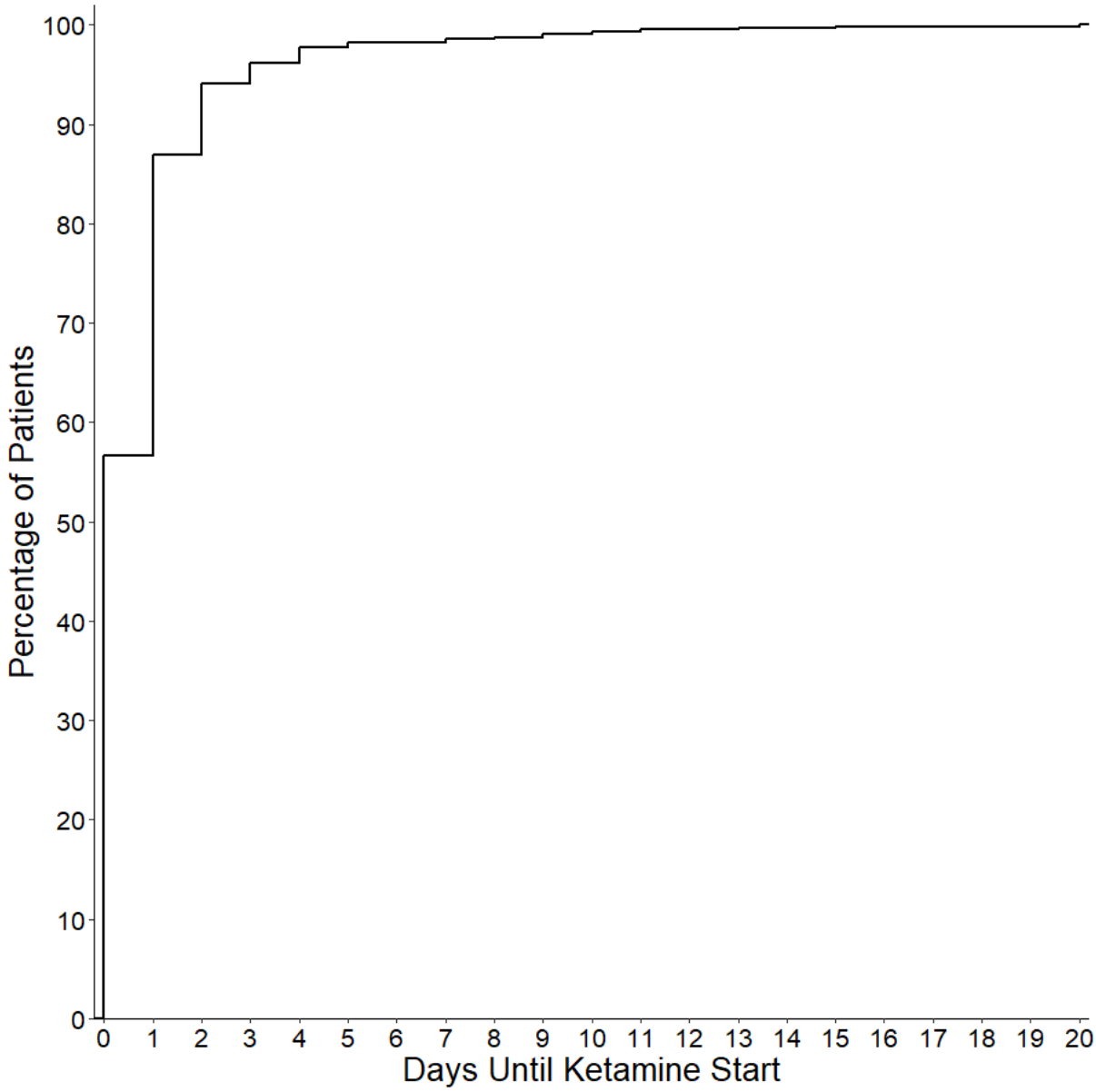
	Absolute Risk, % (95% CI)	Risk Difference, % (95% CI)	Risk Ratio (95% CI)
Full course of follow-up			
Natural course	7.38 (6.81 to 8.08)	1 (Reference)	1 (Reference)
Never received low dose ketamine	6.29 (5.73 to 6.92)	RD, -1.09 (-1.35 to -0.86)	0.85 (0.82 to 0.88)
Always received low dose ketamine	26.56 (22.63 to 30.66)	RD, 19.18 (15.38 to 22.95)	3.60 (3.07 to 4.14)
Treatment from day 1 to 5			
Natural course	7.38 (6.81 to 8.08)	1 (Reference)	1 (Reference)
Never received low dose ketamine	6.49 (5.95 to 7.13)	RD, -0.89 (-1.11 to -0.69)	0.88 (0.85 to 0.91)
Always received low dose ketamine	21.58 (18.67 to 24.75)	RD, 14.19 (11.31 to 17.16)	2.92 (2.52 to 3.33)
Treatment from day 5 to 10			
Natural course	7.38 (6.81 to 8.08)	1 (Reference)	1 (Reference)
Never received low dose ketamine	7.24 (6.68 to 7.96)	RD, -0.14 (-0.18 to -0.09)	0.98 (0.98 to 0.99)
Always received low dose ketamine	12.67 (11.56 to 14.15)	RD, 5.29 (4.35 to 6.47)	1.72 (1.60 to 1.87)
Treatment from day 10 to 15			
Natural course	7.38 (6.81 to 8.08)	1 (Reference)	1 (Reference)
Never received low dose ketamine	7.35 (6.77 to 8.05)	RD, -0.03 (-0.06 to -0.01)	1.00 (0.99 to 1.00)
Always received low dose ketamine	8.84 (8.17 to 9.73)	RD, 1.46 (1.22 to 1.81)	1.20 (1.16 to 1.25)
Treatment from day 1 to 2			
Natural course	7.38 (6.81 to 8.08)	1 (Reference)	1 (Reference)
Never received low dose ketamine	6.57 (6.01 to 7.20)	-0.81 (-1.03 to -0.64)	0.89 (0.86 to 0.91)
Always received low dose ketamine	18.27 (15.90 to 20.96)	10.88 (8.91 to 13.51)	2.47 (2.18 to 2.81)
Treatment from day 1 to 3			
Natural course	7.38 (6.81 to 8.08)	1 (Reference)	1 (Reference)
Never received low dose ketamine	6.55 (5.98 to 7.18)	-0.84 (-1.06 to -0.66)	0.89 (0.86 to 0.91)
Always received low dose ketamine	19.93 (17.27 to 22.95)	12.54 (10.14 to 15.21)	2.70 (2.34 to 3.08)
Treatment from day 1 to 4			
Natural course	7.38 (6.81 to 8.08)	1 (Reference)	1 (Reference)
Never received low dose ketamine	6.50 (5.96 to 7.15)	-0.88 (-1.09 to -0.68)	0.88 (0.85 to 0.91)
Always received low dose ketamine	20.84 (18.03 to 23.96)	13.45 (10.79 to 16.30)	2.82 (2.44 to 3.22)
Treatment from day 10 to 11			
Natural course	7.38 (6.81 to 8.08)	1 (Reference)	1 (Reference)
Never received low dose ketamine	7.36 (6.78 to 8.06)	-0.02 (-0.04 to -0.01)	1.00 (0.99 to 1.00)
Always received low dose ketamine	8.49 (7.81 to 9.33)	1.10 (0.89 to 1.41)	1.15 (1.12 to 1.19)
Treatment from day 10 to 12			
Natural course	7.38 (6.81 to 8.08)	1 (Reference)	1 (Reference)
Never received low dose ketamine	7.36 (6.78 to 8.06)	-0.02 (-0.05 to -0.01)	1.00 (0.99 to 1.00)
Always received low dose ketamine	8.60 (7.92 to 9.47)	1.22 (0.98 to 1.55)	1.16 (1.14 to 1.21)
Treatment from day 10 to 13			
Natural course	7.38 (6.81 to 8.08)	1 (Reference)	1 (Reference)
Never received low dose ketamine	7.36 (6.78 to 8.06)	-0.02 (-0.05 to -0.01)	1.00 (0.99 to 1.00)
Always received low dose ketamine	8.67 (7.99 to 9.55)	1.29 (1.06 to 1.63)	1.17 (1.14 to 1.22)

Abbreviations: CI is confidence interval.

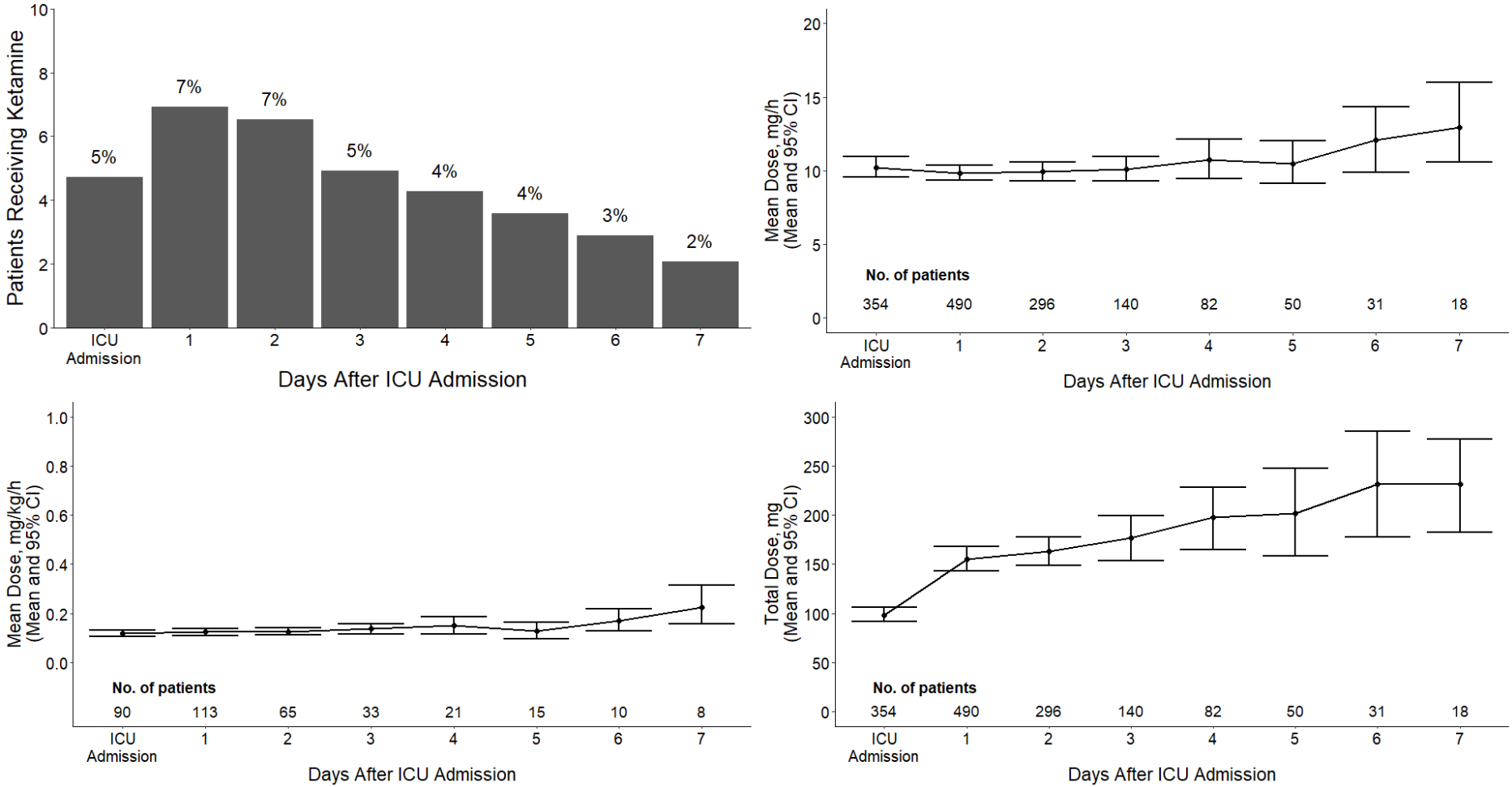
eFigure 1 – Flowchart of Patients



eFigure 2 – Days Until Ketamine Start

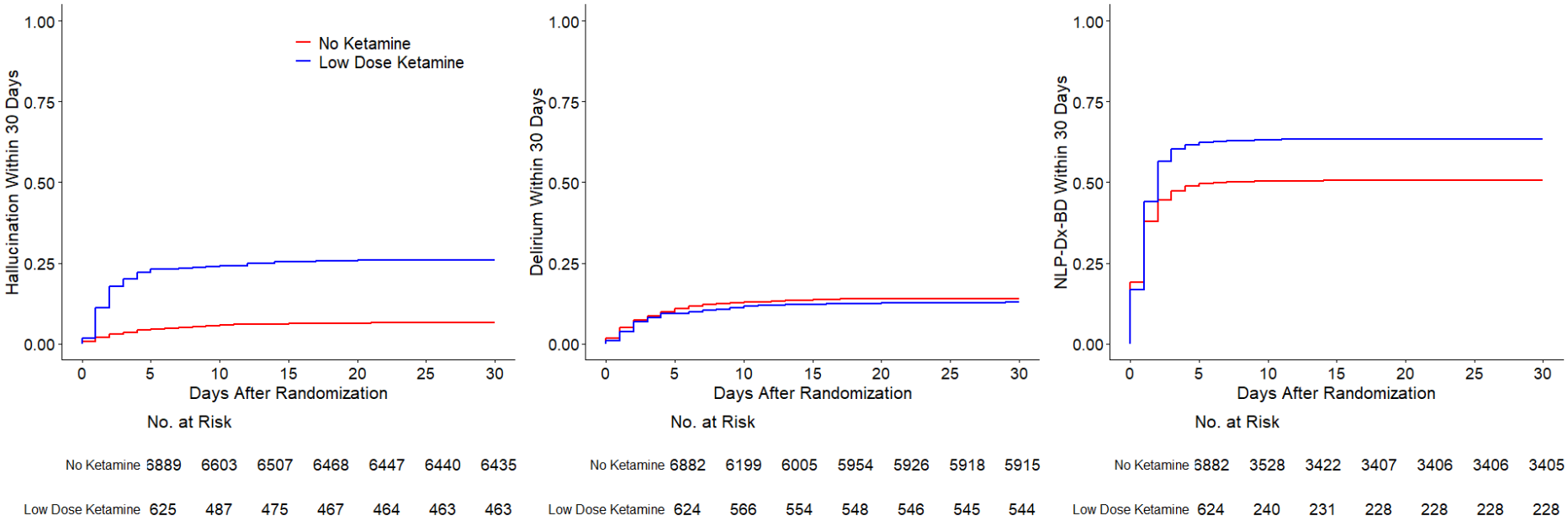


eFigure 3 – Use of Low Dose Ketamine During the First Seven Days of ICU Stay



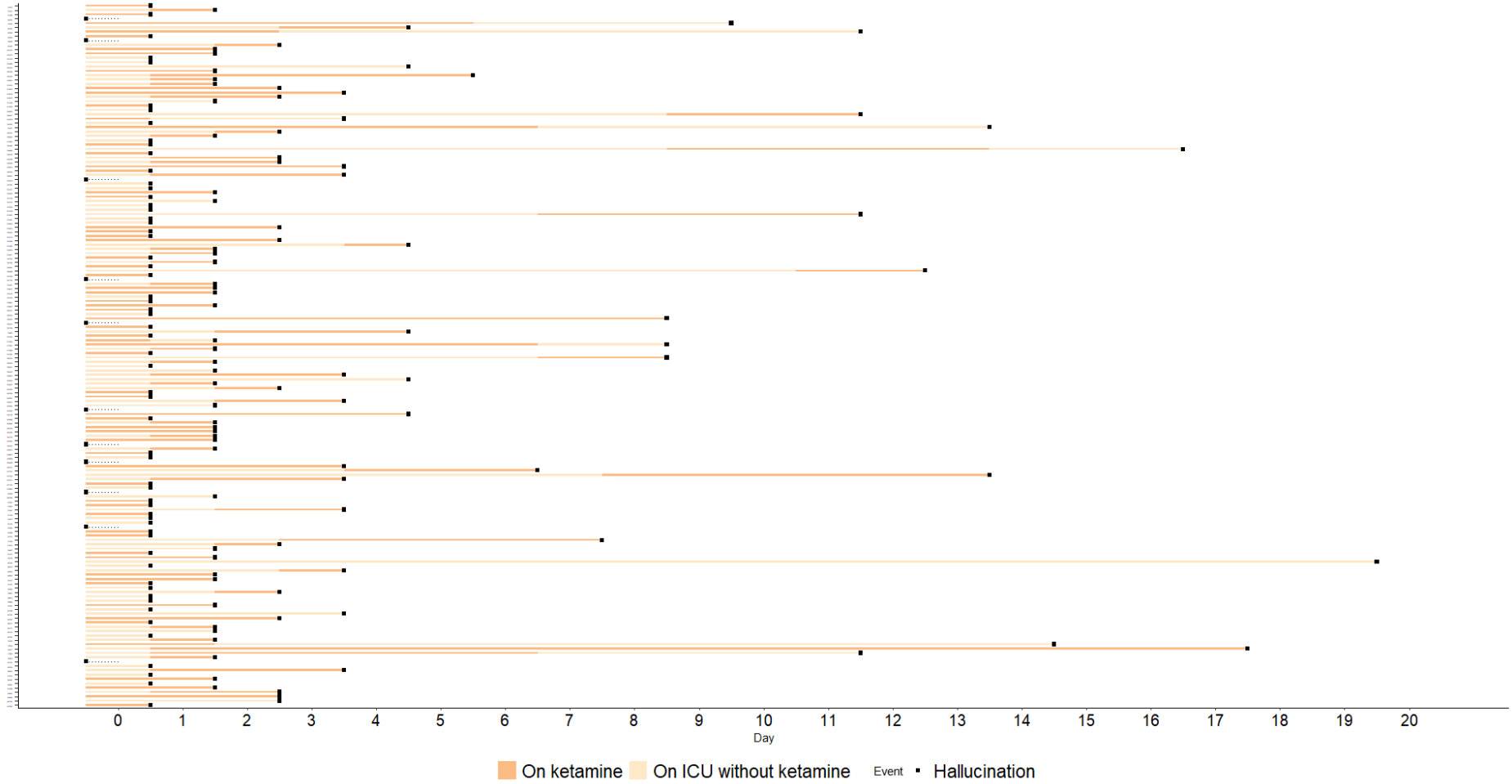
Top Left, percentage of patients receiving low dose ketamine in each day of follow-up after ICU admission.
Top Right, mean daily dose of ketamine in mg/h. Circles are mean and error bars are 95% confidence intervals.
Bottom Left, mean daily dose of ketamine per kilogram in mg/kg/h. Circles are mean and error bars are 95% confidence intervals. Less patients are reported in this plot due to missing data in weight.
Bottom Right, total daily dose of ketamine in mg. Circles are mean and error bars are 95% confidence intervals.

eFigure 4 – Development of Hallucinations, Delirium and NLP-Dx-BD within 30 Days According to the Use of Low Dose Ketamine



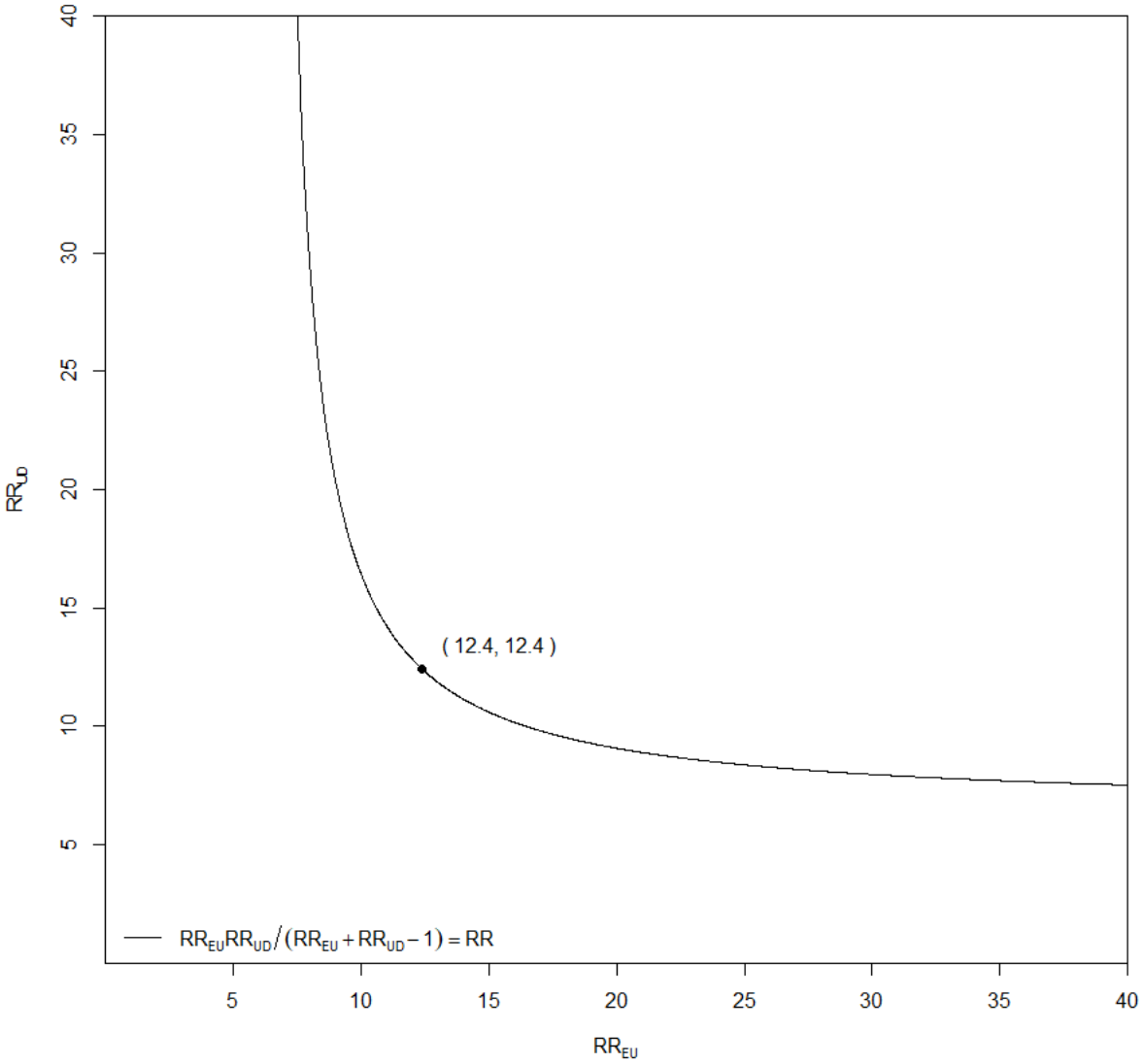
Kaplan-Meier curves with patients who did not develop the outcome of interest censored at day 30.

eFigure 5 – Relationship Between Low Dose Ketamine Use and Development of Hallucination



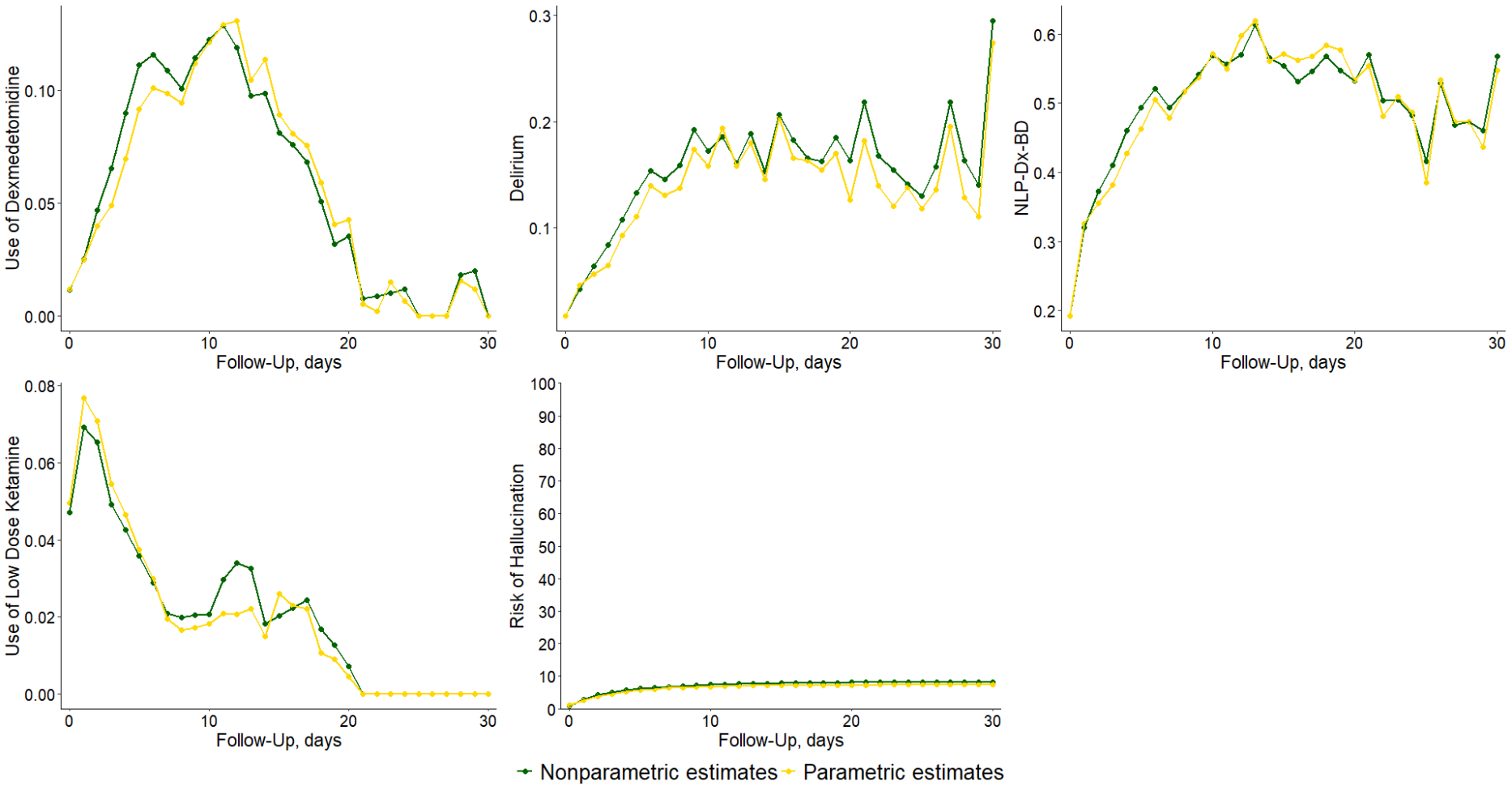
For each patient, the colours in the line represent the use (or not) of low dose ketamine of the patient over time. A solid square at the end of a line indicates that the patient developed hallucination.

eFigure 6 – E-Value for The Association Between Low Dose Ketamine and Hallucinations in the Main Model



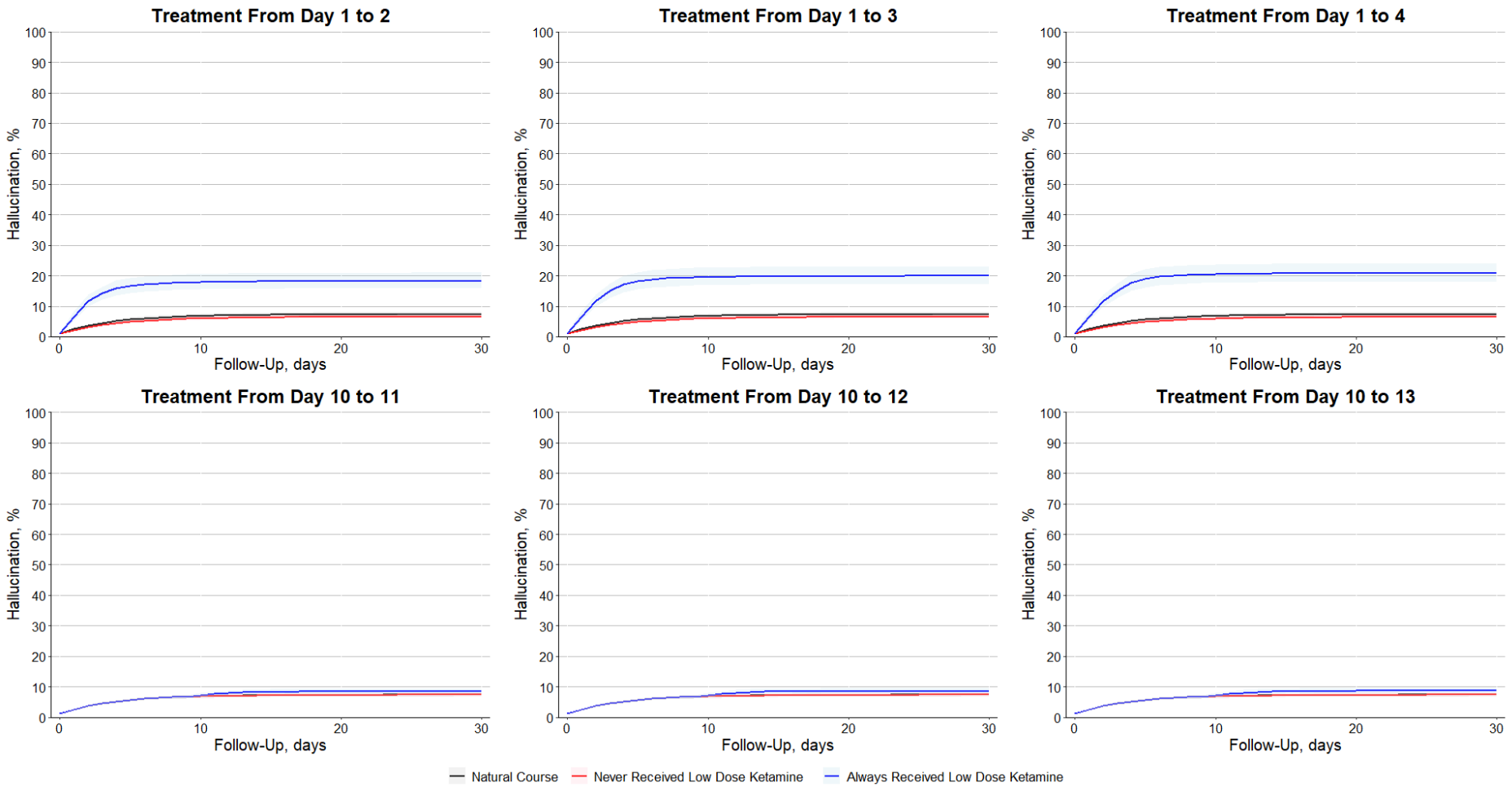
A risk ratio of 6.46 (5.17 to 8.07) was found in the main model, and the E-value of 12.39 illustrates that a relatively strong, unmeasured confounder associated with both hallucination and the treatment strategy would be required to explain away the estimate.

eFigure 7 – Parametric Versus Nonparametric Estimate of Covariates and Risk of Hallucinations Under Natural Course During Follow-Up



Comparable parametric versus nonparametric estimates of the covariates were reported for the natural course, suggesting correct model specification for the parametric g-formula.

eFigure 8 – Estimated Risk of Hallucinations Within 30 Days Under Different Treatment Strategies with Varying Initiation Timing and Duration of Treatment



Estimates from parametric g-formula. Shaded areas are 95% confidence interval. RD is risk difference and RR is risk ratio.