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Corticosteroids and Transition to Delirium in Acute Lung Injury: Multinomial Logistic Regression Analysis Accounting for Multiple States

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In Devlin et. al.'s editorial (1) on our publication evaluating the association of corticosteroids with transitioning from a "normal" (i.e. non-comatose and non-delirious) state to a delirious state,(2) they noted our exclusion of the competing transitions to coma, intensive care unit (ICU) discharge and death, raising the question of "overestimation of the risk for delirium associated with corticosteroid administration."(1)

To address this question, we used a first order Markov model(3) to estimate the probability of transitioning from a normal, delirious or comatose state on a given day to one of the following 5 states on the next day: normal, delirious, comatose, ICU discharge or death. This model included all consecutive days with delirium or coma assessments, and was fit using a multinomial logistic regression model with robust variance estimates that included the 12 exposure variables in our original multivariable analysis.(2) We allowed the association of corticosteroids (and other exposure variables) with transition to a delirious state to vary based on the subject's prior state (normal vs. comatose) using statistical interaction terms.

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In our original analysis,(2) estimating the probability of transitioning from a normal state to a delirious state (reported as 14% (2)) was not the primary goal, instead our focus was on the association of corticosteroids with this transition. When analyzing the data to consider all possible states, as suggested by Devlin et al.,(1) this probability was modestly lower at 11% (see bolded value in Table 1). The complete set of transition probabilities (Table 1), also demonstrates the high probability of delirium when transitioning out of a comatose state. Of 2397 days in which a patient was comatose on the prior day, in 1865 (78%) days patients remained comatose and in 106 (4%) they transitioned to death. In the remaining 426 days where survivors transitioned out of coma, 389 (91%) transitioned to delirium, with only 30 (7%) transitioning to a normal state and 7 (2%) being discharged from ICU.

In Table 2, we report our original results(2) versus results from the expanded statistical analysis as previously described. The primary exposure variable, systematic corticosteroids administered on the prior day, was significantly associated with transition to delirium with an odds ratio (95% confidence interval [CI]) of 1.46 (1.02, 2.11, $p=0.04$) that was very similar to the originally reported value of 1.52 (1.05, 2.21, $p=0.03$) (2). Therefore, the similar estimate produced by the expanded model, accounting for all states, suggests that the original results did not overestimate the association of corticosteroids with the transition from a normal to a delirious state.

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Table 1

Transition probabilities for all possible states from an initial day (day T) to the next day (day T+1)

	Normal on Day T+1	Delirium on Day T+1	Coma on Day T+1	ICU Discharge on Day T+1	ICU Death on Day T+1	Total ^a
Normal on Day T	634 (72%)	99 (11%)	12 (1%)	131 (15%)	1 (0%)	877 (100%)
Delirium on Day T	211 (11%)	1348 (71%)	253 (13%)	77 (4%)	12 (1%)	1901 (100%)
Coma on Day T	30 (1%)	389 (16%)	1865 (78%)	7 (0%)	106 (4%)	2397 (100%)
Total	875	1836	2130	215	119	5175

ICU=Intensive Care Unit

^aRow percentages may not add to 100% due to rounding

Table 2

Patient and ICU variables associated with transition to delirium from a prior normal state

Variable	Original analysis using logistic regression model(2)		New analysis using multinomial regression model	
	OR (95% CI) ^a	P-Value	OR (95 % CI) ^a	P-Value
Age <40 years old	Reference		Reference	
Age 40–60 years old	1.81 (1.26, 2.62)	<0.01	1.91 (1.31, 2.77)	<0.01
Age >60 years old	2.52 (1.65, 3.87)	<0.01	2.66 (1.70, 4.16)	<0.01
Male	1.34 (0.96, 1.86)	0.08	1.27 (0.91, 1.79)	0.16
Caucasian Race	0.74 (0.53, 1.02)	0.06	0.72 (0.52, 0.99)	0.05
Home use of opioids	1.11 (0.97, 1.27)	0.12	1.12 (0.98, 1.28)	0.10
APACHE II(4) at ICU admission	1.01 (1.00, 1.03)	0.31	1.01 (0.99, 1.03)	0.23
Daily SOFA Organ Failure score ^b	1.03 (0.99, 1.07)	0.11	1.03 (1.00, 1.07)	0.06
Daily sepsis status	1.06 (0.79, 1.41)	0.71	1.06 (0.80, 1.42)	0.67
Corticosteroid administration	1.52 (1.05, 2.21)	0.03	1.46 (1.02, 2.11)	0.04
Higher corticosteroid dose (per 40 mg of prednisone- equivalent in 24 hr)	0.97 (0.86, 1.08)	0.57	1.00 (0.92, 1.09)	0.94
Benzodiazepine administration	1.32 (0.93, 1.89)	0.12	1.24 (0.87, 1.77)	0.23
Higher benzodiazepine dose (per 5 mg midazolam- equivalent in 24 hr)	1.03 (0.98, 1.09)	0.18	1.02 (0.99, 1.05)	0.15

APACHE = Acute Physiology and Chronic Health Evaluation; SOFA=Sequential Organ Failure Assessment; OR=Odds Ratio, CI=Confidence Interval, ICU=Intensive Care Unit

^aOdds ratios are interpreted as the odds of transition to a delirious state from a normal state given the characteristic (for a binary variable) or given a one unit increase (for continuous variable) when all other characteristics remain constant.

^b Sequential Organ Failure Assessment score(5) is modified to exclude the neurologic component to prevent adjusting for a component of the primary outcome within the regression model.