**Keppra Study Report R-168**

**5. One last request, while looking over the data I noticed some of the numbers for the doses of Keppra received didn't make sense. I fixed these for both groups and if you could compare them again I'd appreciate it! They're in column J on both sheets.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Behavioral Event** | | **P-Value** |
| **No (n=512)** | **Yes (n=453)** |
| **Age at Admission (SD)** | 59.41 (18.49) | 60.87 (18.63) | 0.221 |
| **Ethnicity (%)** |  |  | 0.486 |
| Black or African American | 233 (45.5) | 191 (42.2) |  |
| Other | 20 ( 3.9) | 23 ( 5.1) |  |
| Unknown | 9 ( 1.8) | 5 ( 1.1) |  |
| White | 250 (48.8) | 234 (51.7) |  |
| **Gender (%)** |  |  | >0.999 |
| Male | 267 (52.1) | 237 (52.3) |  |
| Female | 245 (47.9) | 216 (47.7) |  |
| **Diagnosis (%)** |  |  | 0.418 |
| Cerebral infarction | 141 (27.5) | 111 (24.5) |  |
| Intracerebral hemorrhage | 155 (30.3) | 147 (32.5) |  |
| Subarachnoid hemorrhage | 78 (15.2) | 59 (13.0) |  |
| Traumatic intracranial injury | 138 (27.0) | 136 (30.0) |  |
| **GCS (IQR)** | 14.00 (7-15) | 13.00 (7-15) | 0.825 |
| **Discharge Disposition (%)** |  |  | <0.001 |
| Discharged to Rehab Unit/Facility | 77 (15.0) | 108 (23.8) |  |
| Discharged to SNF | 72 (14.1) | 130 (28.7) |  |
| Expired | 110 (21.5) | 50 (11.0) |  |
| Home | 213 (41.6) | 109 (24.1) |  |
| Hospice | 14 ( 2.7) | 33 ( 7.3) |  |
| Other | 26 ( 5.1) | 23 ( 5.1) |  |
| log(**Length of Stay at Hospital**) (SD) | 2.04 (1.02) | 2.56 (0.90) | <0.001 |
| log(**Length of Stay in ICU**) (SD) | 1.55 (1.10) | 1.99 (1.03) | <0.001 |
| log(**Total** **Keppra Dose**) (SD) | 0.96 (0.41) | 1.14 (0.39) | <0.001 |
| Log(**Keppra Duration**) (SD) | 0.73 (0.36) | 0.90 (0.36) | <0.001 |
| **Length of Stay at Hospital (IQR)** | 12.33 (3.80-16.60) | 13.91 (7.01-23.61) | <0.001 |
| **Length of Stay in ICU (IQR)** | 4.4 (2.00-11.10) | 7.6 (3.6-16.1) | <0.001 |
| **Total Keppra Dose (IQR)** | 11.0 (5.0-15.0) | 14.0 (10.0-21.0) | <0.001 |
| **Keppra Duration (IQR)** | 5.10 (2.22-7.0) | 6.59 (4.53-10.49) | <0.001 |
| **Rass < 3 (%)** |  |  | 0.002 |
| Yes | 229 (44.7) | 248 (54.7) |  |
| No |  |  |  |
| **Median Keppra Dose (%)** |  |  |  |
| 250 | 9 ( 1.8) | 7 ( 1.5) |  |
| 500 | 330 (64.5) | 278 (61.4) |  |
| 750 | 72 (14.1) | 76 (16.8) |  |
| 1000 | 72 (14.1) | 60 (13.2) |  |
| 1250 | 0 ( 0.0) | 2 ( 0.4) |  |
| 1500 | 22 ( 4.3) | 20 ( 4.4) |  |
| 1750 | 0 ( 0.0) | 1 ( 0.2) |  |
| 2000 | 4 ( 0.8) | 9 ( 2.0) |  |
| 3000 | 1 ( 0.2) | 0 ( 0.0) |  |
| Missing | 2 ( 0.4) | 0 ( 0.0) |  |
| **Received Benzos (%)** |  |  | < 0.001 |
| Yes | 175 (34.2) | 216 (47.7) |  |
| No | 337 (65.8) | 237 (52.3) |  |
| **CIWA Orders (%)** |  |  | < 0.001 |
| Yes | 50 (9.8) | 119 (26.3) |  |
| No | 462 (90.2) | 334 (73.7) |  |
| **Pain Scores (%)** |  |  | 0.236 |
| 0-3 | 360 (70.3) | 335 (74) |  |
| 4-10 | 152 (29.7) | 118 (26.0) |  |
| **Received IV opioid (%)** |  |  | 0.361 |
| Yes | 391 (76.4) | 358 (79.0) |  |
| No | 121 (23.6) | 95 (21.0) |  |
| **AED received while on Keppra (%)** |  |  | 0.002 |
| Yes | 56 (10.9) | 83 (18.3) |  |
| No | 456 (89.1) | 370 (81.7) |  |

**4. When looking over the data I noticed that about twice any many people died in the group without a behavioral adverse event. Would it be possible to include an evaluation of length of ICU and hospital stays as well as doses received only in the surviving patients?**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Behavioral Event** | | **P-Value** |
| **No (n=402)** | **Yes (n=403)** |
| log(**Length of Stay at Hospital**) (SD) | 0.96 (0.40) | 1.13 (0.37) | <0.001 |
| log(**Length of Stay in ICU**) (SD) | 0.71 (0.46) | 0.88 (0.44) | <0.001 |
| log(**Total** **Keppra Dose**) (SD) | 1.01 (0.37) | 1.14 (0.38) | <0.001 |
| Log(**Keppra Duration**) (SD) | 0.77 (0.34) | 0.90 (0.35) | <0.001 |
| **Length of Stay at Hospital (IQR)** | 9.54 (4.68-18.50) | 14.19 (7.15-24.05) | <0.001 |
| **Length of Stay in ICU (IQR)** | 4.90 (2.00-12.60) | 7.40 (3.60-16.20) | <0.001 |
| **Total Keppra Dose (IQR)** | 13.00 (7.00-15.00) | 14.00 (10.00-20.00) | <0.001 |
| **Keppra Duration (IQR)** | 5.97 (2.84-7.07) | 6.59 (4.60-10.03) | <0.001 |

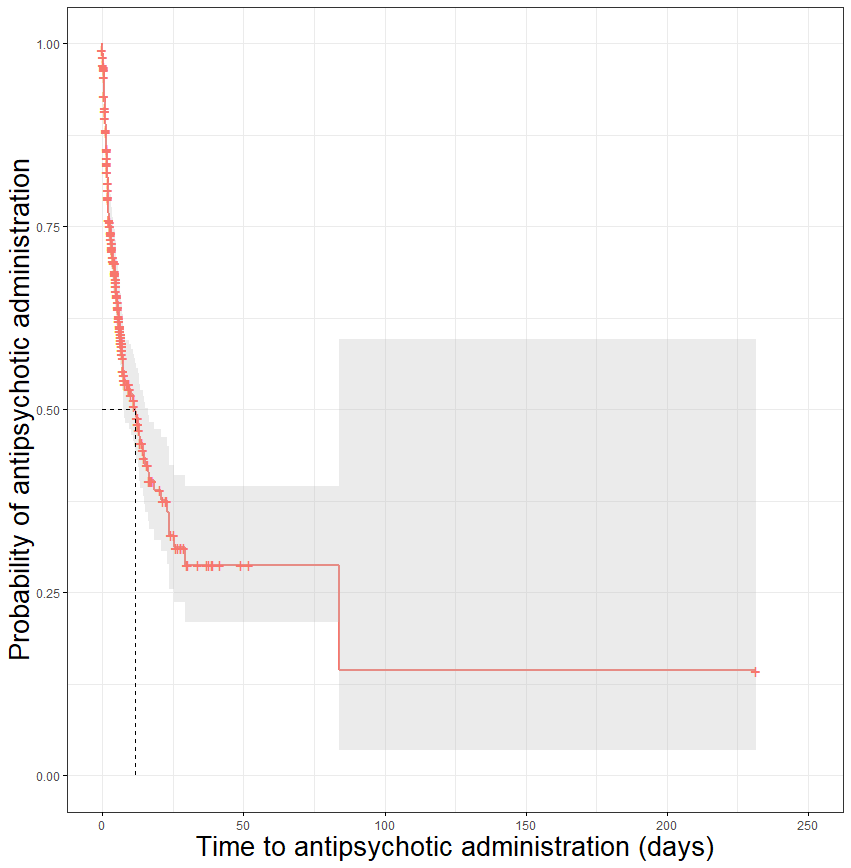
**1. Establishing a median time to:**

**A. antipsychotic administration (Column N) B. Positive CAM-ICU (Column P) and C. Overall median time depending on if an antipsychotic was administered first or a positive CAM-ICU was recorded first in patients who had both an antipsychotic and positive CAM-ICU**

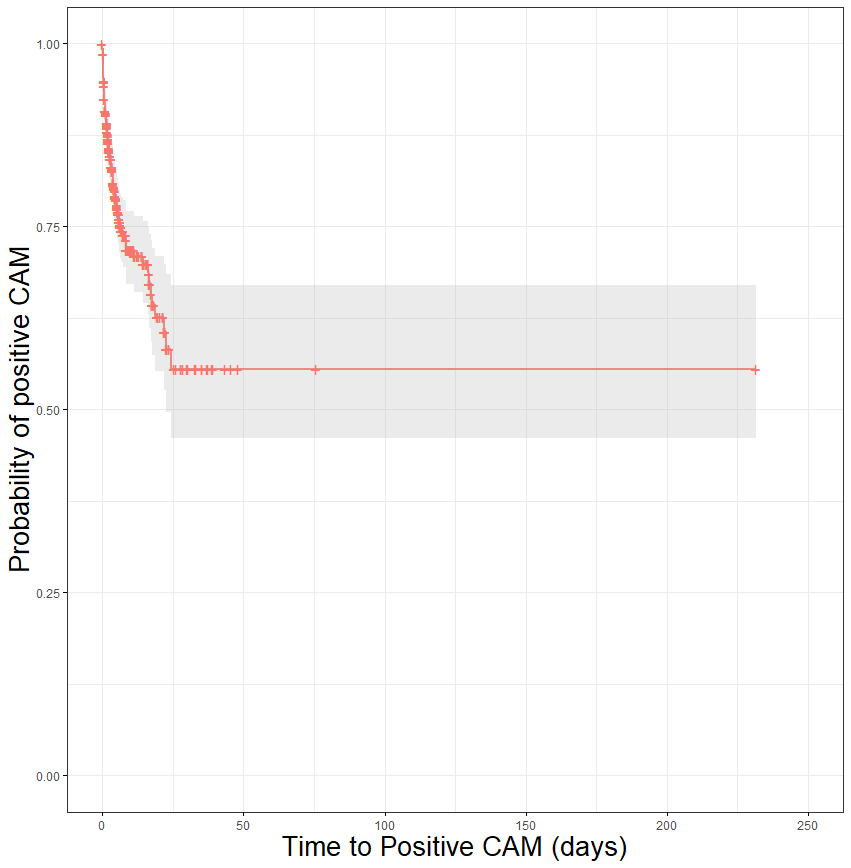
* **Patients that experienced a behavioral event (excluding missing):**
* Median time to antipsychotic administration (IQR): 2.15 (1.15-5.38)
* Median time to positive CAM (IQR): 2.04 (0.62-4.42)
* Median time to first occurrence (N=50) (IQR): 1.5 (0.62-3.90)

**2. In reference to the above we also discussed including the overall time patients were observed (duration of Keppra therapy) for those who did not receive an antipsychotic or have a positive CAM-ICU. These values are in column Q. I also included in the overall duration of Keppra therapy for the patients who did have a positive CAM-ICU or received an antipsychotic in this is needed. Additionally, the overall duration of Keppra therapy is in column K for the patients without a behavioral adverse event.**

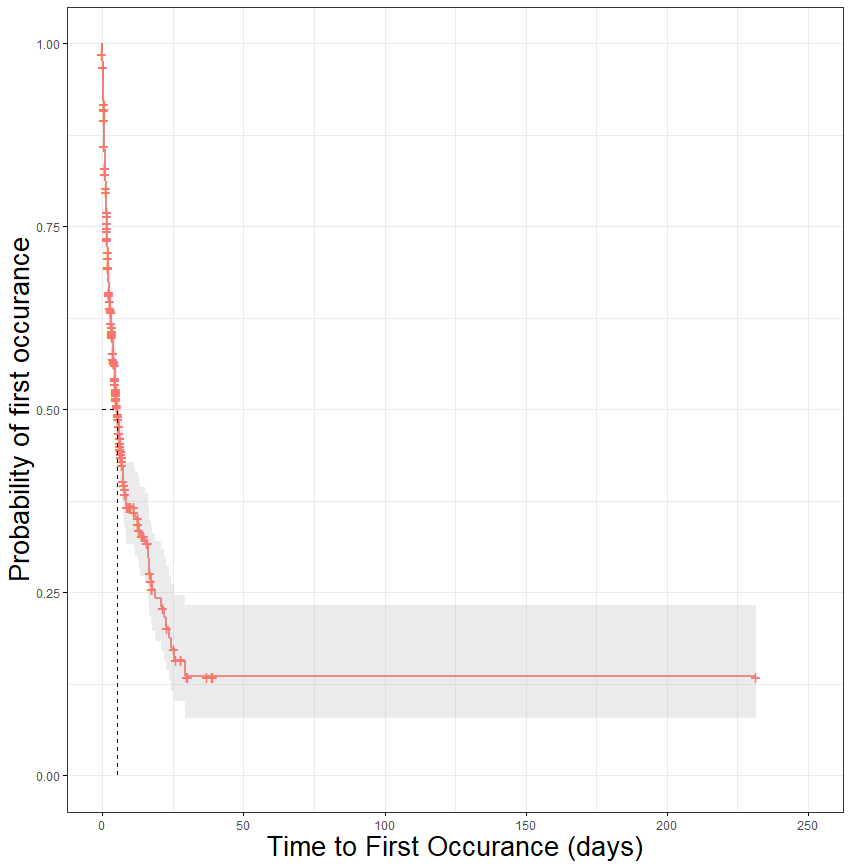
* **Patients that experienced a behavioral event (including missing (censored)):**
* Estimated median time to antipsychotic administration (95% CI): 11.74 (7.53-16.35)



* Estimated median time to positive CAM (95% CI): NA



* Estimated median time to first occurrence (all patients) (95% CI): 5.33 (4.39-6.44)



**3. The other thing we discussed was evaluating for confounding variables. The confounding variables we would like to evaluate are in columns T through AA for patients with a behavioral adverse event and columns L through S for patients without a behavioral adverse event. These variables include RASS </= -3 (yes or no based on occurence), median Keppra dose (in mg), receipt of benzodiazepine (yes/no based on occurence), CIWA orders (yes/no based on occurence), median pain score (0-3 represents no or mild pain, 4-10 represents moderate to severe pain), receipt of IV opioid (yes/no based on occurence), concurrent AED (yes/no based on occurence), and if a patient did receive another AED that drug/drugs.**

**Multiple Logistic Regression Parameter Estimates:**

|  |  |  |  |
| --- | --- | --- | --- |
| **Potential Confounder** | **Estimate** | **Std. Error** | **P-Value** |
| Intercept | -0.572 | 0.164 | <0.001 |
| Rass < 3 (Yes) | 0.356 | 0.151 | 0.018 |
| Received Benzo (Yes) | 0.228 | 0.146 | 0.118 |
| CIWA Orders (Yes) | 1.131 | 0.194 | < 0.001 |
| Pain Score (4-10) | -0.107 | 0.156 | 0.495 |
| Received IV opioid (Yes) | -0.082 | 0.172 | 0.634 |
| Concurrent AED (Yes) | 0.464 | 0.196 | 0.018 |
| Median Keppra Dose (>500) | 0.061 | 0.142 | 0.667 |

**Odds Ratios:**

|  |  |
| --- | --- |
| **Potential Confounder** | **Odds Ratio (95% CI)** |
| Intercept | 0.56 (0.41, 0.78) |
| Rass < 3 (Yes) | 1.43 (1.06, 1.92) |
| Received Benzo (Yes) | 1.26 (0.94, 1.67) |
| CIWA Orders (Yes) | 3.10 (2.13, 4.56) |
| Pain Score (4-10) | 0.90 (0.66, 1.22) |
| Received IV opioid (Yes) | 0.92 (0.66, 1.29) |
| Concurrent AED (Yes) | 1.59 (1.08, 2.34) |
| Median Keppra Dose (>500) | 1.06 (0.80, 1.40) |

Notes:

* The above multiple logistic regression model, models the probability of a behavioral event having been occurred while adjust for the above variables.
* Prior to modelling, the Median Keppra Dose variable was recategorized at <=500 mg and > 500 mg. This was due to the fact that it was not a continuous variable (given that it only took a select number of values), yet it had too many levels with very few frequencies (see first table)
* 2 patients had incorrect values for Median Keppra Dose, they were removed prior to modelling
* After modelling we see that the Rass < 3, CIWA orders, and concurrent AED variables are significant at the 0.05 level (parameter estimates table), meaning that they have a confounding effect on the probability of a behavioral event
* The interpretation of the odds ratios are as follows:

The odds of having a behavioral event is 43% higher for patients that had Rass < 3 than for patients that had Rass >= 3. Similar interpretations can be made for the other confounders.