**Keppra Study Report R-168**

1. **Inclusion of all patient demographics of surviving patients.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Stratified by Behavioral Event | | P-Value |
| Variable | No (N=402) | Yes (N=369) |  |
| Age (mean (SD)) | 58.07 (18.51) | 60.34 (18.99) | 0.091 |
| Ethnicity (%) |  |  | 0.420 |
| White | 198 (49.3) | 191 (51.8) |  |
| Black or African American | 183 (45.5) | 157 (42.5) |  |
| Other | 15 ( 3.7) | 18 ( 4.9) |  |
| Unknown | 6 ( 1.5) | 3 ( 0.8) |  |
| Gender (%) |  |  | 0.805 |
| Male | 210 (52.2) | 197 (53.4) |  |
| Female | 192 (47.8) | 172 (46.6) |  |
| Diagnosis (%) |  |  | 0.081 |
| CEREBRAL INFARCTION | 115 (28.6) | 89 (24.1) |  |
| INTRACEREBRAL HEMORRHAGE | 121 (30.1) | 117 (31.7) |  |
| SUBARACHNOID HEMORRHAGE | 69 (17.2) | 49 (13.3) |  |
| Traumatic intracranial injury | 97 (24.1) | 114 (30.9) |  |
| GCS (mean (SD)) | 11.78 (4.00) | 11.33 (4.21) | 0.128 |
| Discharge.Disposition (%) |  |  | <0.001 |
| Disch to Rehab Unit/Facility | 77 (19.2) | 98 (26.6) |  |
| Disch to SNF | 72 (17.9) | 123 (33.3) |  |
| Home | 213 (53.0) | 98 (26.6) |  |
| Hospice | 14 ( 3.5) | 29 ( 7.9) |  |
| Other | 26 ( 6.5) | 21 ( 5.7) |  |
| Length of Stay Hospital (mean (SD)) | 13.64 (14.53) | 21.38 (31.54) | <0.001 |
| Length of Stay ICU (mean (SD)) | 9.00 (11.12) | 13.87 (28.22) | 0.001 |
| Total Keppra Doses (mean (SD)) | 14.44 (13.34) | 20.82 (21.79) | <0.001 |
| Keppra Duration (mean (SD)) | 7.08 (7.89) | 11.02 (16.31) | <0.001 |
| log Length of Stay Hospital (mean (SD)) | 0.96 (0.40) | 1.15 (0.37) | <0.001 |
| log Length of Stay ICU (mean (SD)) | 0.71 (0.46) | 0.89 (0.44) | <0.001 |
| log Total Keppra Doses (mean (SD)) | 1.01 (0.37) | 1.17 (0.38) | <0.001 |
| log Keppra Duration (mean (SD)) | 0.77 (0.34) | 0.92 (0.35) | <0.001 |
| Rass less than -3 (%) |  |  | <0.001 |
| Yes | 123 (30.6) | 195 (52.8) |  |
| No | 279 (69.4) | 174 (47.2) |  |
| Median Keppra Dose (%) |  |  | NaN |
| 250 | 7 ( 1.7) | 5 ( 1.4) |  |
| 500 | 264 (65.7) | 226 (61.2) |  |
| 750 | 55 (13.7) | 62 (16.8) |  |
| 1000 | 53 (13.2) | 50 (13.6) |  |
| 1250 | 0 ( 0.0) | 1 ( 0.3) |  |
| 1500 | 19 ( 4.7) | 17 ( 4.6) |  |
| 1750 | 0 ( 0.0) | 1 ( 0.3) |  |
| 2000 | 4 ( 1.0) | 7 ( 1.9) |  |
| 3000 | 0 ( 0.0) | 0 ( 0.0) |  |
| Received Benzo (%) |  |  | <0.001 |
| Yes | 143 (35.6) | 186 (50.4) |  |
| No | 259 (64.4) | 183 (49.6) |  |
| CIWA Orders (%) |  |  | <0.001 |
| Yes | 45 (11.2) | 107 (29.0) |  |
| No | 357 (88.8) | 262 (71.0) |  |
| Pain Scores (%) |  |  | 0.012 |
| 0-3 | 144 (35.8) | 100 (27.1) |  |
| 4-10 | 258 (64.2) | 269(73.9) |  |
| Received IV opioid (%) |  |  | 0.130 |
| Yes | 295 (73.4) | 289 (78.3) |  |
| No | 107 (27.6) | 80 (21.7) |  |
| AED Received while on Keppra (%) |  |  | 0.010 |
| Yes | 45 (11.2) | 74 (20.1) |  |
| No | 357 (88.8) | (79.9) |  |
| Times RASS less neg3 (mean (SD)) | 34.87 (60.06) | 20.33 (27.95) | 0.004 |
| Percent RASS less neg3 (mean (SD)) | 23.42 (26.07) | 14.96 (22.44) | 0.002 |

1. **Possibility of enlarging or adding X-axis break for time to event curves.**

Need more clarification on this

1. **Is it possible to adjust for the confounding variables and look at the different lengths of stay for each group (behavioral event vs no behavioral event) using a regression analysis?**

Multiple linear regression analysis modelling the mean change in length of stay (hospital/ICU) between patients that had a behavioral event and those that did, after adjusting for RASS, Benzo status, pain score, opioid status, concurrent AED status, and Keppra dose

* Hospital length of stay:

|  |  |  |  |
| --- | --- | --- | --- |
| Parameter | Estimate | Std. Error | P-Value |
| Intercept | 0.51170 | 0.03157 | < 0.0001 |
| Behavioral Event (Yes) | 0.18124 | 0.02535 | < 0.0001 |
| Rass < -3 (Yes) | 0.08894 | 0.02787 | 0.0015 |
| Received Benzo (Yes) | 0.15593 | 0.02614 | < 0.0001 |
| Pain Scores (4-10) | 0.01459 | 0.02877 | 0.61215 |
| Received IV opioid (Yes) | 0.32759 | 0.03177 | < 0.0001 |
| Concurrent AED (Yes) | 0.12494 | 0.03552 | 0.0005 |
| Median Keppra Dose cat (>500 mg) | 0.03881 | 0.0261 | 0.1373 |

* ICU length of stay

|  |  |  |  |
| --- | --- | --- | --- |
| Parameter | Estimate | Std. Error | P-Value |
| Intercept | 0.24130 | 0.03397 | < 0.0001 |
| Behavioral Event (Yes) | 0.12935 | 0.02727 | < 0.0001 |
| Rass < -3 (Yes) | 0.15855 | 0.02998 | < 0.0001 |
| Received Benzo (Yes) | 0.22019 | 0.02812 | < 0.0001 |
| Pain Scores (4-10) | 0.01543 | 0.03096 | 0.6183 |
| Received IV opioid (Yes) | 0.34756 | 0.03418 | < 0.0001 |
| Concurrent AED (Yes) | 0.08933 | 0.03821 | 0.0196 |
| Median Keppra Dose cat (>500 mg) | 0.02171 | 0.02808 | 0.4396 |

Notes:

* The above analyses models the log of the length of stay (given the skewness; lack of normality) using the following regression equation:

log(yi) = β0 + β1X1 + β2X2 + … + εi

* The interpretation for behavioral event is a follows:
* The difference in the expected geometric means of the log of hospital length of stay between patients with a behavioral event and those without is 0.175, while adjusting for all other covariates.
* The natural way to interpret log transformed outcomes is to use exponentiate:
* Patients with a behavioral event had a 20% (exp(0.18124)= 1.1987) increase in the geometric mean of hospital length of stays, while adjusting for all other covariates.
* The interpretation for ICU length of stay is similar.

1. **Since there is a link between CIWA orders and benzo use, removing CIWA orders as a confounding variable**

Multiple Logistic Regression Parameter Estimates:

|  |  |  |  |
| --- | --- | --- | --- |
| **Potential Confounder** | **Estimate** | **Std. Error** | **P-Value** |
| Intercept | -0.70083 | 0.16952 | <0.0001 |
| Rass < -3 (Yes) | 0.40396 | 0.15206 | 0.0078 |
| Received Benzo (Yes) | 0.56163 | 0.14086 | <0.0001 |
| Pain Score (4-10) | -0.05967 | 0.15887 | 0.7070 |
| Received IV opioid (Yes) | -0.04631 | 0.17601 | 0.7924 |
| Concurrent AED (Yes) | 0.54216 | 0.1944 | 0.0052 |
| Median Keppra Dose (>500) | 0.06017 | 0.14323 | 0.6744 |

Odds Ratios:

|  |  |
| --- | --- |
| **Potential Confounder** | **Odds Ratio (95% CI)** |
| Intercept | 0.496 (0.355, 0.690) |
| Rass < -3 (Yes) | 1.498 (1.112, 2.020) |
| Received Benzo (Yes) | 1.754 (1.331, 2.313) |
| Pain Score (4-10) | 0.942 (0.689, 1.286) |
| Received IV opioid (Yes) | 0.955 (0.676, 1.350) |
| Concurrent AED (Yes) | 1.720 (1.177, 2.525) |
| Median Keppra Dose (>500) | 1.062 (0.801, 1.406) |

1. **Is it possible to incorporate the confounding variables in the time to event curves?**

Time to antipsychotic administration:

* Cox Proportional Hazard Ratio Estimates:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Parameter | HR | Lower 95% CI | Lower 95% CI | P-Value |
| Rass < -3 (Yes) | 0.74 | 0.53 | 1.10 | 0.087 |
| Received Benzo (Yes) | 1.30 | 0.96 | 1.76 | 0.079 |
| Pain Score (4-10) | 0.97 | 0.69 | 1.37 | 0.901 |
| Received IV opioid (Yes) | 0.60 | 0.45 | 0.97 | 0.033 |
| Concurrent AED (Yes) | 1.21 | 0.86 | 1.70 | 0.264 |
| Median Keppra Dose (>500) | 0.89 | 0.66 | 1.21 | 0.476 |

Time to positive CAM:

* Cox Proportional Hazard Ratio Estimates:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Parameter | HR | Lower 95% CI | Lower 95% CI | P-Value |
| Rass < -3 (Yes) | 2.33 | 1.41 | 3.84 | 0.001 |
| Received Benzo (Yes) | 0.82 | 0.56 | 1.21 | 0.335 |
| Pain Score (4-10) | 0.83 | 0.51 | 1.34 | 0.451 |
| Received IV opioid (Yes) | 0.50 | 0.29 | 0.87 | 0.014 |
| Concurrent AED (Yes) | 0.74 | 0.45 | 1.21 | 0.231 |
| Median Keppra Dose (>500) | 1.06 | 0.72 | 1.55 | 0.759 |

Notes: The cox proportional hazards model evaluates the effect of multiple variables on the time to event (antipsychotic administration/positive CAM). In other words, it allows us to examine how specified factors influence the rate of a particular event happening (e.g., infection, death) at a particular point in time. We measure this using the hazard ratio (HR).

* The interpretation for RASS is a follows:

There is a significant relationship between RASS < -3 and higher risk of being administered an antipsychotic. Specifically, having RASS < -3 increases the risk of being administered an antipsychotic by a factor of 2.33 (or 133%), while holding all other covariates constant.

* Similar interpretations can be made about the other HRs and about time to positive CAM